

At the high dose (1.2 µg), the glycoPEGylated rFSH had somewhat higher *in vivo* activity than the unPEGylated rFSH.

### G-CSF

#### 28. GlycoPEGylation of G-CSF produced in CHO cells

**Preparation of Asialo-Granulocyte-Colony Stimulation Factor (G-CSF).** G-CSF produced in CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, 5 mM CaCl<sub>2</sub> and concentrated to 500 µL in a Centricon Plus 20 centrifugal filter. The solution is incubated with 300 mU/mL Neuraminidase II (*Vibrio cholerae*) for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel performed. The reaction mixture is then added to prewashed N-(*p*-aminophenyl)oxamic acid-agarose conjugate (800 µL/mL reaction volume) and the washed beads gently rotated for 24 hours at 4 °C. The mixture is centrifuged at 10,000 rpm and the supernatant was collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer and once with 0.2 mL of the Tris-EDTA buffer and all supernatants are pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub> and then twice more against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub>. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter and stored at -20 °C. The conditions for the IEF gel were run according to the procedures and reagents provided by Invitrogen. Samples of native and desialylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of G-CSF-(α2,3)-Sialyl-PEG.** Desialylated G-CSF was dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST3Gal1 at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis

according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of G-CSF-(alpha2,8)-Sialyl-PEG.** G-CSF produced in CHO cells, which contains an alpha2,3-sialylated O-linked glycan, is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of CST-II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction has CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of G-CSF-(alpha2,6)-Sialyl-PEG.** G-CSF, containing only O-linked GalNAc, is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST6GalNAcII or II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction has CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

G-CSF produced in CHO cells was treated with Arthrobacter sialidase and was then purified by size exclusion on Superdex75 and was treated with ST3Gal1 or ST3Gal2 and then with CMP-SA-PEG 20Kda. The resulting molecule was purified by ion exchange and

gel filtration and analysis by SDS PAGE demonstrated that the PEGylation was complete. This is the first demonstration of glycoPEGylation of an O-linked glycan.

#### Glucocerebrosidase

##### 29. Glucocerebrosidase-mannose-6-phosphate produced in CHO cells

This example sets forth the procedure to glycoconjugate mannose-6-phosphate to a peptide produced in CHO cells such as glucocerebrosidase.

**Preparation of asialo-glucoceramide.** Glucocerebrosidase produced in CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, and is incubated with 300 mU/mL sialidase-agarose conjugate for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel and SDS-PAGE performed according to Invitrogen procedures. The mixture is centrifuged at 10,000 rpm and the supernatant is collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer, and once with 0.2 mL of the Tris-EDTA buffer. All supernatants are pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris-HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub> and then twice more against 50 mM Tris-HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub>. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

##### **Preparation of Glucocerebrosidase-SA-linker-Mannose-6-phosphate (procedure**

**1).** Asialo-glucocerebrosidase from above is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-linker-Man-6-phosphate and 0.1 U/mL of ST3Gal3 at 32°C for 2 days. To monitor the incorporation of sialic acid-linker-Man-6-phosphate, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas TSK-Gel-3000 analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using

SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of Glucocerebrosidase-SA-linker-Mannose-6-phosphate (procedure**

2). Glucocerebrosidase, produced in CHO but incompletely sialylated, is dissolved at 2.5  
5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated  
with 1 mM CMP-sialic acid-linker-Man-6-phosphate and 0.1 U/mL of ST3Gal3 at 32°C for 2  
days. To monitor the incorporation of sialic acid-linker-Man-6-phosphate, a small aliquot of  
the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the  
peptide is separated from the free label by gel filtration on a Toso Haas TSK-Gel-3000  
10 analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the  
peptide is quantitated using an in-line fluorescent detector. When the reaction is complete,  
the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using  
PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the  
reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and  
15 reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by  
MALDI-TOF MS.

**30. Glucocerebrosidase-transferrin**

This example sets forth the procedures for the glycoconjugation of proteins, and in  
20 particular, transferrin is glycoconjugated to glucocerebrosidase. The GlcNAc-ASN structures  
are created on glucoceraminidase, and Transferrin-SA-Linker-Gal-UDP is conjugated to  
GNDF GlcNAc-ASN structures using galactosyltransferase.

**Preparation of GlcNAc-glucocerebrosidase (Cerezyme™). Cerezyme™**

(glucocerebrosidase) produced in CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM  
25 Tris-HCl pH 7.4, 0.15 M NaCl, and is incubated with 300 mU/mL Endo-H-agarose conjugate  
for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with  
the appropriate buffer and a IEF gel and SDS-PAGE performed according to Invitrogen  
procedures. The mixture is centrifuged at 10,000 rpm and the supernatant is collected. The  
beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer and  
30 once with 0.2 mL of the Tris-EDTA buffer and all supernatants are pooled. The supernatant  
is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub> and then twice

more against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub>. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of Transferrin-SA-Linker-Gal-glucocerebrosidase.** Transferrin-SA-Linker-Gal-UDP from above is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl<sub>2</sub>, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 2.5 mg/mL GlcNAc-glucocerebrosidase and 0.1 U/mL of galactosyltransferase at 32°C for 2 days. To monitor the incorporation of glucocerebrosidase, the peptide is separated by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1) and the product detected by UV absorption. The reaction mixture is then purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

### GM-CSF

#### 31. Generation and PEGylation of GlcNAc-ASN Structures: GM-CSF produced in *Saccharomyces*

This example sets forth the preparation of Tissue-type Activator with PEGylated GlcNAc-Asn structures.

Recombinant GM-CSF expressed in yeast is expected to contain 2 N-linked and 2 O-linked glycans. The N-linked glycans should be of the branched mannan type. This recombinant glycoprotein is treated with an endoglycosidase from the group consisting of endoglycosidase H, endoglycosidase-F1, endoglycosidase-F2, endoglycosidase-F3, endoglycosidase-M either alone or in combination with mannosidases I, II and III to generate GlcNAc nubs on the asparagine (Asn) residues on the peptide/protein backbone.

The GlcNAc-Asn structures on the peptide/protein backbone is then be modified with galactose or galactose-PEG using UDP-galactose or UDP-galactose-6-PEG, respectively, and a galactosyltransferase such as GalT1. In one case the galactose-PEG is the terminal residue.

In the second case the galactose is further modified with SA-PEG using a CMP-SA-PEG donor and a sialyltransferase such as ST3GalIII. In another embodiment the GlcNAc-Asn structures on the peptide/protein backbone can be galactosylated and sialylated as described above, and then further sialylated using CMP-SA-PEG and an  $\alpha$ 2,8-sialyltransferase such as the enzyme encoded by the *Campylobacter jejuni* cst-II gene.

### Herceptin<sup>TM</sup>

#### 32. Glycoconjugation of mithramycin to Herceptin<sup>TM</sup>

This example sets forth the procedures to glycoconjugate a small molecule, such as mithramycin to Fc region glycans of an antibody molecule produced in mammalian cells. Here, the antibody Herceptin<sup>TM</sup> is used, but one of skill in the art will appreciate that the method can be used with many other antibodies.

**Preparation of Herceptin<sup>TM</sup>-Gal-linker-mithramycin.** Herceptin<sup>TM</sup> is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl<sub>2</sub>, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM UDP-galactose-linker-mithramycin and 0.1 U/mL of galactosyltransferase at 32°C for 2 days to introduce the mithramycin in the Fc region glycans. To monitor the incorporation of galactose, a small aliquot of the reaction has <sup>14</sup>C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The fractions containing product are combined, concentrated, buffer exchanged and then freeze-dried. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Interferon  $\alpha$  and Interferon  $\beta$ 33. GlycoPEGylation of Proteins expressed in Mammalian or Insect Systems:  
EPO, Interferon  $\alpha$  and Interferon  $\beta$ 

This example sets forth the preparation of PEGylated peptides that are expressed in  
5 mammalian and insect systems.

**Preparation of acceptor from mammalian expression systems.** The peptides to be glycoPEGylated using CMP-sialic acid PEG need to have glycans terminating in galactose. Most peptides from mammalian expression systems will have terminal sialic acid that first  
needs to be removed.

10 **Sialidase digestion.** The peptide is desialylated using a sialidase. A typical procedure involves incubating a 1 mg/mL solution of the peptide in Tris-buffered saline, pH 7.2, with 5 mM  $\text{CaCl}_2$  added, with 0.2 U/mL immobilized sialidase from *Vibrio cholera* (Calbiochem) at 32°C for 24 hours. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. The resin is then removed by centrifugation or  
15 filtration, and then washed to recover entrapped peptide. At this point, EDTA may be added to the solution to inhibit any sialidase that has leached from the resin.

**Preparation from insect expression systems.** EPO, interferon-alpha, and interferon-beta may also be expressed in non-mammalian systems such as yeast, plants, or insect cells. The peptides to be glycoPEGylated using CMP-sialic acid PEG need to have  
20 glycans terminating in galactose. The majority of the N-glycans on peptides expressed in insect cells, for example, are the trimannosyl core. These glycans are first built out to glycans terminating in galactose before they are acceptors for sialyltransferase.

**Building acceptor glycans from trimannosyl core.** Peptide (1 mg/mL) in Tris-buffered saline, pH 7.2, containing 5 mM  $\text{MnCl}_2$ , 5 mM UDP-glcNAc, 0.05 U/mL  
25 GLCNACT I, 0.05 U/mL GLCNACT II, is incubated at 32°C for 24 hours or until the reaction is substantially complete. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. After buffer exchange to remove UDP and other small molecules, UDP-galactose and  $\text{MnCl}_2$  are each added to 5 mM, galactosyltransferase is added to 0.05 U/mL, and is incubated at 32°C for 24H or until the reaction is substantially  
30 complete. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. The peptides are then ready for glycoPEGylation.

**Building O-linked glycans.** A similar strategy may be employed for interferon alpha to produce enzymatically the desired O-glycan Gal-GalNAc. If necessary, GalNAc linked to serine or threonine can be added to the peptide using appropriate peptide GalNAc transferases (e.g. GalNAc T1, GalNAc T2, T3, T4, etc. ) and UDP-GalNAc. Also, if needed,  
5 galactose can be added using galactosyltransferase and UDP-galactose.

**GlycoPEGylation using sialyltransferase.** The glycopeptides (1 mg/mL) bearing terminal galactose in Tris buffered saline + 0.02% sodium azide are incubated with CMP-SA-PEG (0.75 mM) and 0.4 U/mL sialyltransferase (ST3Gal3 or ST3Gal4 for N-glycans on EPO and interferon beta; ST3Gal4, or ST3Gal1 for O-glycans on interferon alpha) at 32°C for 24  
10 hours. Other transferases that may work include the 2,6 sialyltransferase from *Photobacterium damsella*. The acceptor peptide concentration is most preferably in the range of 0.1 mg/mL up to the solubility limit of the peptide. The concentration of CMP-SA-PEG should be sufficient for there to be excess over the available sites, but not so high as to cause peptide solubility problems due to the PEG, and may range from 50 µM up to 5 mM, and the  
15 temperature may range from 2°C up to 40°C. The time required for complete reaction will depend on the temperature, the relative amounts of enzyme to acceptor substrate, the donor substrate concentration, and the pH.

#### 34. GlycoPEGylation of Interferon α produced in CHO cells

**Preparation of Asialo-Interferon α.** Interferon alpha produced from CHO cells is  
20 dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, 5 mM CaCl<sub>2</sub> and concentrated to 500 µL in a Centricon Plus 20 centrifugal filter. The solution is incubated with 300 mU/mL Neuraminidase II (*Vibrio cholerae*) for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a  
25 IEF gel performed. The reaction mixture is then added to prewashed N-(p-aminophenyl)oxamic acid-agarose conjugate (800 µL/mL reaction volume) and the washed beads gently rotated for 24 hours at 4 °C. The mixture is centrifuged at 10,000 rpm and the supernatant was collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer and once with 0.2 mL of the Tris-EDTA buffer and all  
30 supernatants were pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub> and then twice more against 50 mM Tris -HCl pH 7.4, 1 M



NaCl, 0.05% NaN<sub>3</sub>. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter and stored at -20 °C. The conditions for the IEF gel are run according to the procedures and reagents provided by Invitrogen. Samples of native and desialylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

5        **Preparation of Interferon-alpha-(alpha2,3)-Sialyl-PEG.** Desialylated interferon-alpha is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST3Gal1 at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide  
10 is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF  
15 analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and desialylated Interferon-alpha are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of Interferon-alpha-(alpha2,8)-Sialyl-PEG.** Interferon-alpha produced in CHO, which contains an alpha2,3-sialylated O-linked glycan, is dissolved at 2.5  
20 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of CST-II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction has CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free  
25 label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and  
30 PEGylated interferon-alpha are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of Interferon-alpha-(alpha2,6)-Sialyl-PEG.** Interferon-alpha, containing only O-linked GalNAc, was dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST6GalNAcI or II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated interferon-alpha are dialyzed against water and analyzed by MALDI-TOF MS.

35. GlycoPEGylation of Interferon- $\beta$ -1a with PEG (10 kDa) and PEG (20 kDa)

This example illustrates a procedure PEGylate Interferon- $\beta$  with either PEG (10 kDa) or PEG (20 kDa).

Briefly, Interferon- $\beta$ -1a (INF- $\beta$ ) was obtained from Biogen (Avonex<sup>TM</sup>). The INF- $\beta$  was first purified by Superdex-75 chromatography. The INF- $\beta$  was then desialylated with *Vibrio cholerae* sialidase. The INF- $\beta$  was then PEGylated with SA-PEG (10 kDa) or SA-PEG (20 kDa) and purified with Superdex-200 chromatography.

**Superdex-75 chromatography purification.** INF- $\beta$  (150  $\mu$ g) was applied to a Superdex-75 column (Amersham Biosciences, Arlington Heights, IL) and eluted with PBS with 0.5 M NaCl, 0.02 Tween-20, 20 mM histidine and 10% glycerol. The eluant was monitored for absorbance at 280 nm (Figure 172A and 172B) and fractions were collected. Peaks 4 and 5 were pooled, concentrated in an Amicon Ultra 15 spin filter (Millipore, Billerica, MA), and the buffer was exchanged to TBS with 5 mM CaCl<sub>2</sub>, 0.02% Tween-20, 20 mM histidine and 10% glycerol.

**Sialidase Reaction.** The INF- $\beta$  was then desialylated with *Vibrio cholera* sialidase (70 mU/ml, CALBIOCHEM®, EMD Biosciences, Inc., San Diego, CA) on agarose in TBS

with 5 mM CaCl<sub>2</sub>, 0.02% Tween-20, 20 mM histidine and 10% glycerol. The reaction was carried out at 32°C for 18 hours. The INF- $\beta$  was removed from the agarose with a 0.22  $\mu$ m Spin-X™ filter (Corning Technology, Inc., Norcross, GA). Figure 173A depicts the MALDI analysis of glycans released from native INF- $\beta$ . The native INF- $\beta$  has many glycoforms containing terminal sialic acid moieties. Figure 173B depicts the MALDI analysis of glycans released from desialylated INF- $\beta$ . The desialylated INF- $\beta$  has primarily one glycoform which is bi-antennary with terminal galactose moieties.

**Lectin Dot-Blot Analysis of Sialylation.** Samples of the INF- $\beta$  from the desialidase reaction were dot-blotted onto nitrocellulose and then blocked with Tris buffered saline (TBS: 0.05M Tris, 0.15M NaCl, pH 7.5) and DIG kit (glycan differentiation kit available from Roche #1 210 238) blocking buffer. Some of the blots were incubated with *Maackia amurensis* agglutinin (MAA) labeled with digoxigenin (DIG) (Roche Applied Science, Indianapolis, IL) to detect  $\alpha$ 2,3-sialylation of INF- $\beta$ . These blots were washed with TBS then incubated with anti-digoxigenin antibody labeled with alkaline phosphatase, then washed again with TBS and developed with NBT/X-phosphate solution, wherein NBT is 4-nitro blue tetrazolium chloride and X-phosphate is 5-bromo-4-chloro-3-indoyl phosphate. The left side of Figure 174 depicts the results of the MAA blot of INF- $\beta$  after the desialylation reaction. The INF- $\beta$  is partially desialylated, as indicated by the decrease in dot development as compared to native INF- $\beta$  in the desialylated samples.

Other blots were incubated with *Erthrina cristagalli* lectin (ECL) labeled with biotin (Vector Laboratories, Burlingame, CA) to detect exposed galactose residues on INF- $\beta$ . After incubation with 2.5  $\mu$ g/ml ECL, the blots were washed in TBS and incubated with streptavidin labeled with alkaline phosphatase. The blots were then washed again and developed. The right side of Figure 174 depicts the ECL blot after development. The increased intensity of the dot of desialylated INF- $\beta$  as compared to the native INF- $\beta$  indicate more exposed galactose moieties and therefore extensive desialylation.

**PEGylation of Desialylated INF- $\beta$  with SA-PEG (10 kDa).** Desialylated INF- $\beta$  (0.05 mg/ml) was PEGylated with ST3Gal3 (50 mU/ml) and CMP-SA-PEG (10 kDa) (250  $\mu$ M) in an appropriate buffer of TBS + 5 mM CaCl<sub>2</sub>, 0.02% Tween 20, 20 mM histidine, 10%

glycerol for 50 hours at 32°C. Figure 175 depicts the SDS-PAGE analysis of the reaction products showing PEGylated INF- $\beta$  at approximately 98 kDa.

**PEGylation of Desialylated INF- $\beta$  with SA-PEG (20 kDa).** Desialylated INF- $\beta$  (0.5 mg/ml) was PEGylated with ST3Gal3 (170 mU/ml) and CMP-SA-PEG (20 kDa) in an appropriate buffer of TBS + 5 mM CaCl<sub>2</sub>, 0.02% Tween 20, 20 mM histidine, 10% glycerol for 50 hours at 32°C. Figure 176 depicts the SDS-PAGE analysis the products of the PEGylation reaction. The PEGylated INF- $\beta$  has many higher molecular weight bands not found in the unmodified INF- $\beta$  indicating extensive PEGylation.

**Superdex-200 Purification of INF- $\beta$  PEGylated with PEG (10 kDa).** The products of the PEGylation reaction were separated on a Superdex-200 column (Amersham Biosciences, Arlington Heights, IL) in PBS with 0.5 NaCl, 0.02 Tween-20, 20 mM histidine and 10% glycerol at 1ml/min and 30 cm/hr flow. The eluant was monitored for absorbance at 280 nm (Figure 177) and fractions were collected. Peaks 3 and 4 were pooled and concentrated in an Amicon Ultra 15 spin filter.

**Bioassay of INF- $\beta$  PEGylated with PEG (10 kDa).**

The test is inhibition of the proliferation of the lung carcinoma cell line, A549. The A549 cell line are lung carcinoma adherent cells growing in RPMI + 10% FBS at 37°C 5% CO<sub>2</sub>. They can be obtained from ATCC # CCL-185. Wash the cells with 10 ml of PBS and remove the PBS. Add 5 ml of trypsin, incubate for 5 minutes at room temperature or 2 minutes at 37°C. When the cells are detached resuspend into 25 ml of media and count the cells. Dilute the cells at a concentration of 10000 cells/ml and add 200  $\mu$ l / well (96 wells plate). Incubate for 4 hours at 37°C 5% CO<sub>2</sub>. Prepare 1 ml of IFN  $\beta$  at a concentration of 0.1  $\mu$ g/ml. Filter it under the hood with a 0.2  $\mu$ m filter. Add 100  $\mu$ l per well (8 replicates = 1 lane). Incubate for 3 days (do not let the cells go to confluence). Remove 200  $\mu$ l of media (only 100 $\mu$ l per well left). Add 25  $\mu$ l of MTT (Sigma) (5 mg/ml filtered 0.22 $\mu$ m). Incubate for 4 hours at 37°C and 5% CO<sub>2</sub>. Aspirate the media gently and add 100  $\mu$ l of a mixture of isopropanol (100 ml and 6N HCl. Aspirate up and down to homogenize the crystal violet. Read OD 570nm (remove the background at 630 or 690 nm).

Figure 178 depicts the results of the bioassay of the peaks containing INF- $\beta$  PEGylated with PEG (10 kDa) as eluted from the Superdex-200 column.

**Superdex-200 Purification of INF- $\beta$  PEGylated with PEG (20 kDa).** The products of the PEG (20 kDa) PEGylation reaction were separated on a Superdex-200 column (Amersham Biosciences, Arlington Heights, IL) in PBS with 0.5 NaCl, 0.02 Tween-20, 20 mM histidine and 10% glycerol at 1 ml/min flow. The eluant was monitored for absorbance at 280 nm (Figure 179) and fractions were collected. Peak 3 contained most of the INF- $\beta$  PEGylated with PEG (20 kDa).

**Endotoxin test of INF- $\beta$  PEGylated with PEG (20 kDa).**

Limulus Lysate Test was performed, BioWhittaker # 50-647U

**Table 24.** Results of the endotoxin test of INF- $\beta$  PEGylated with PEG (20 kDa).

|                                | Concentration |            |                   |
|--------------------------------|---------------|------------|-------------------|
| INF- $\beta$ with PEG (20 kDa) | 10 EU/ml      | 0.06 mg/ml | 0.16 EU/ $\mu$ g  |
| INF- $\beta$ with PEG (20 kDa) | 1 EU/ml       | 0.07 mg/ml | 0.014 EU/ $\mu$ g |
| Native INF- $\beta$            | 40 EU/ml      | 0.1 mg/ml  | 0.4 EU/ $\mu$ g   |

Remicade<sup>TM</sup>

36. GlycoPEGylation of Remicade<sup>TM</sup> antibody

This example sets forth the procedure to glycoPEGylate a recombinant antibody molecule by introducing PEG molecules to the Fc region glycans. Here Remicade<sup>TM</sup>, a TNF-R:IgG Fc region fusion protein, is the exemplary peptide.

**Preparation of Remicade<sup>TM</sup>-Gal-PEG (10 kDa).** Remicade<sup>TM</sup> is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl<sub>2</sub>, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM UDP-galactose-PEG (10 kDa) and 0.1 U/mL of galactosyltransferase at 32°C for 2 days to introduce the PEG in the Fc region glycans. To monitor the incorporation of galactose, a small aliquot of the reaction has <sup>14</sup>C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The fractions containing product are combined, concentrated, buffer

exchanged and then freeze-dried. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

#### Rituxan™

##### 37. Glycoconjugation of geldanamycin to Rituxan™

This example sets forth the glycoconjugation of a small molecule, such as geldanamycin, to the Fc region glycans of an antibody produced in CHO cells, such as Rituxan™. Here, the antibody Rituxan™ is used, but one of skill in the art will appreciate that the method can be used with many other antibodies.

**Preparation of Rituxan™-Gal-linker-geldanamycin.** Rituxan™ is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl<sub>2</sub>, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 1 mM UDP-galactose-linker-geldanamycin and 0.1 U/mL of galactosyltransferase at 32°C for 2 days to introduce the geldanamycin in the Fc region glycans. To monitor the incorporation of galactose, a small aliquot of the reaction has <sup>14</sup>C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The fractions containing product are combined, concentrated, buffer exchanged and then freeze-dried. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

#### Rnase

##### 38. Remodeling high mannose N-glycans to hybrid and complex N-glycans: Bovine pancreatic RNase

This example sets forth the preparation of bovine pancreas RNase with hybrid or complex N-glycans. The high mannose N-linked glycans of the RNase are enzymatically

digested and elaborated to create hybrid N-linked glycans. Additionally, the high mannose N-linked glycans of the RNase are enzymatically digested and elaborated to create complex N-linked glycans.

High mannose structures of *N*-linked oligosaccharides in glycopeptides can be modified to hybrid or complex forms using the combination of  $\alpha$ -mannosidases and glycosyltransferases. This example summarizes the results in such efforts using a simple *N*-Glycan as a model substrate.

Ribonuclease B (RNaseB) purified from bovine pancreas (Sigma) is a glycopeptide consisting of 124 amino acid residues. It has a single potential *N*-glycosylation site modified with high mannose structures. Due to its simplicity and low molecular weight (13.7 kDa to 15.5 kDa), ribonuclease B is a good candidate to demonstrate the feasibility of the *N*-Glycan remodeling from high mannose structures to hybrid or complex *N*-linked oligosaccharides. The MALDI-TOF spectrum of RNaseB (Figure 180A) and HPLC profile for the oligosaccharides cleaved from RNaseB by *N*-Glycanase (Figure 180B) indicated that, other than a small portion of the non-modified peptide, the majority of *N*-glycosylation sites of the peptide are modified with high mannose oligosaccharides consisting of 5 to 9 mannose residues.

**Conversion of high mannose *N*-Glycans to hybrid *N*-Glycans.** High mannose *N*-Glycans were converted to hybrid *N*-Glycans using the combination of  $\alpha$ 1,2-mannosidase, GlcNAcT-I ( $\beta$ -1,2-*N*-acetyl glucosaminyl transferase), GalT-I ( $\beta$ 1,4-galactosyltransferase) and  $\alpha$ 2,3-sialyltransferase /or  $\alpha$ 2,6-sialyltransferase as shown in Figure 181.

As an example, high mannose structures in RNaseB were successfully converted to hybrid structures.

Man<sub>5</sub>GlcNAc<sub>2</sub>-R was obtained from Man<sub>5-9</sub>GlcNAc<sub>2</sub>-R catalyzed by a single  $\alpha$ 1,2-mannosidase cloned from *Trichoderma reesei* (Figure 182). RNase B (1 g, about 67  $\mu$ mol) was incubated at 30°C for 45 hr with 15 mU of the recombinant *T. reesei*  $\alpha$ 1,2-mannosidase in MES buffer (50 mM, pH 6.5) in a total volume of 10 mL. Man<sub>6-9</sub>GlcNAc<sub>2</sub>-protein structures have been successfully converted to Man<sub>5</sub>GlcNAc<sub>2</sub>-protein with high efficiency by the recombinant mannosidase.

Alternately,  $\text{Man}_5\text{GlcNAc}_2\text{-R}$  was obtained from  $\text{Man}_{5,9}\text{GlcNAc}_2\text{-R}$  catalyzed by a single  $\alpha 1,2$ -mannosidase purified from *Aspergillus saitoi* (Figure 183). RNase B (40  $\mu\text{g}$ , about 2.7 nmol) was incubated at  $37^\circ\text{C}$  for 42.5 hr with 25  $\mu\text{U}$  of the commercial *A. saitoi*  $\alpha 1,2$ -mannosidase (Glyko or CalBioChem) in NaOAc buffer (100 mM, pH 5.0) in a total  
5 volume of 20  $\mu\text{l}$ .  $\text{Man}_{6,9}\text{GlcNAc}_2$ -protein structures were successfully converted to  $\text{Man}_5\text{GlcNAc}_2$ -protein by the commercially available mannosidase. However, a new peak corresponding to the GlcNAc-protein appears in the spectrum, indicating the possible contamination of endoglycosidase H in the preparation. Although several mammalian alpha-mannosidases were required to achieve this step, the fungal  $\alpha 1,2$ -mannosidase was very  
10 efficient to remove all  $\alpha 1,2$ -linked mannose residues.

GlcNAcT-I then added a GlcNAc residue to the  $\text{Man}_5\text{GlcNAc}_2\text{-R}$  (Figure 184). The reaction mixture after the *T. reesei*  $\alpha 1,2$ -mannosidase reaction containing RNase B (600  $\mu\text{g}$ , about 40 nmol) was incubated with non-purified recombinant GlcNAcT-I (34 mU) in MES buffer (50 mM, pH 6.5) containing  $\text{MnCl}_2$  (20 mM) and UDP-GlcNAc (5 mM) in a total  
15 volume of 400  $\mu\text{l}$ . at  $37^\circ\text{C}$  for 42 hr. A GlcNAc residue was quantitatively added to  $\text{Man}_5\text{GlcNAc}_2$ -protein by the recombinant GlcNAcT-I.

A Gal residue was then added using GalT 1 (Figure 185). The reaction mixture after the GnT-I reaction containing RNase B (120  $\mu\text{g}$ , about 8 nmol) was incubated at  $37^\circ\text{C}$  for 20 hr with 3.3 mU of the recombinant GalT-1 in Tris-HCl buffer (100 mM, pH 7.3) containing  
20 UDP-Gal (7.5 mM) and  $\text{MnCl}_2$  (20 mM) in a total volume of 100  $\mu\text{l}$ . A Gal residue was added to about 98% of the GlcNAc- $\text{Man}_5\text{GlcNAc}_2$ -protein by the recombinant GalT 1.

The next step was the addition of a sialic acid using an  $\alpha 2,3$ -sialyltransferase or an  $\alpha 2,6$ -sialyltransferase (Figure 186). As an example, ST3Gal III, an  $\alpha 2,3$ -sialyltransferase was used. The reaction mixture after the GalT-1 reaction containing RNase B (13  $\mu\text{g}$ , about 0.87  
25 nmol) was incubated at  $37^\circ\text{C}$  for 16 hr with 8.9 mU of recombinant ST3Gal III in Tris-HCl buffer (100 mM, pH 7.3) containing CMP-Sialic acid (5 mM) and  $\text{MnCl}_2$  (20 mM) in a total volume of 20  $\mu\text{l}$ . A sialic acid residue was added to about 90% of the Gal-GlcNAc- $\text{Man}_5\text{GlcNAc}_2$ -protein by recombinant ST3Gal III using CMP-SA as the donor. The yield can be further improved by adjusting the reaction conditions.



For convenience, no purification or dialysis step was required after each reaction described above. More interesting, GalT 1 and ST3Gal III can be combined in a one-pot reaction. Similar yields were obtained as compared with the separate reactions. The reaction mixture after the GlcNAcT-I reaction containing RNase B (60 µg, about 4 nmol) was

5 incubated at 37°C for 20 hr with 1.7 mU of recombinant GalT 1, 9.8 mU of recombinant ST3Gal III in Tris-HCl buffer (100 mM, pH 7.3) containing UDP-Gal (7.5 mM), CMP-sialic acid (5 mM) and MnCl<sub>2</sub> (20 mM) in a total volume of 60 µl.

As shown in Figure 187, SA-PEG (10 kDa) was successfully added to the RNaseB. The reaction mixture after the GalT-1 reaction containing RNase B (6.7 µg, about 0.45 nmol) 10 was dialyzed against H<sub>2</sub>O for 1 hour at room temperature and incubated at 37°C for 15.5 hours with 55 mU of the recombinant ST3Gal III in Tris-HCl buffer (50 mM, pH 7.3) containing CMP-SA-PEG (10 kDa) (0.25 mM) and MnCl<sub>2</sub> (20 mM) in a total volume of 20 µl. PEG-modified sialic acid residues were successfully added to the Gal-GlcNAc-Man<sub>5</sub>GlcNAc<sub>2</sub>-peptide by the recombinant ST3Gal III. The yield can be further improved by 15 adjusting the reaction conditions.

**Conversion of high mannose N-Glycans to complex N-Glycans.** To achieve this conversion, a GlcNAcβ1,2Man<sub>3</sub>GlcNAc<sub>2</sub>-peptide intermediate is obtained. As shown in Figure 188, there are at least four feasible routes to carry out the reaction from Man<sub>5</sub>GlcNAc<sub>2</sub>-peptide to this intermediate:

20 **Route I:** The Man<sub>5</sub>GlcNAc<sub>2</sub>-peptide produced by the fungal α1,2 mannosidase is a substrate of GlcNAc transferase I (GlcNAcT-I, enzyme 2) which adds one GlcNAc. The terminal α1,3- and α1,6-linked mannose residues of GlcNAcMan<sub>5</sub>GlcNAc<sub>2</sub>-peptide is removed by Golgi α-mannosidase II (ManII, enzyme 5). This route is a part of the natural pathway for the processing of N-linked oligosaccharides carried out in higher organisms.

25 **Route II:** Two mannose residues are first removed by an α-mannosidase (enzyme 6), then a GlcNAc is added by GlcNAcT-I (enzyme 2). Other than its natural acceptor Man<sub>5</sub>GlcNAc<sub>2</sub>-R, GlcNAcT-I can also recognize Man<sub>3</sub>GlcNAc<sub>2</sub>-R as its substrate and add one GlcNAc to the mannose core structure to form GlcNAcMan<sub>3</sub>GlcNAc<sub>2</sub>-peptide.

**Route III:** The α1,6-linked mannose is removed by an α1,6-mannosidase, followed 30 by the addition of GlcNAc by GlcNAcT-I and removal of the terminal α1,3-linked mannose

by an  $\alpha$ 1,3-mannosidase. From the experimental data obtained, GlcNAcT-I can recognize this Man<sub>4</sub>GlcNAc<sub>2</sub>-peptide as acceptor and add one GlcNAc residue to form GlcNAcMan<sub>4</sub>GlcNAc<sub>2</sub>-peptide.

**Route IV:** Similar to Route III,  $\alpha$ 1,3-linked mannose is removed by an  $\alpha$ 1,3-mannosidase, followed by GlcNAcT-I reaction. Then the terminal  $\alpha$ 1,6-linked mannose can be removed by an  $\alpha$ 1,6-mannosidase.

After the function of GlcNAcT-I (responsible for the addition of the GlcNAc  $\beta$ 1,2-linked to the  $\alpha$ 1,3-mannose on the mannose core) and GlcNAcT-II (responsible for the addition of a second GlcNAc  $\beta$ 1,2-linked to the  $\alpha$ 1,6-mannose on the mannose core), the GlcNAc<sub>2</sub>Man<sub>3</sub>GlcNAc<sub>2</sub>-peptide can be processed by GalT 1 and sialyltransferase to form bi-antennary complex N- Glycans. Other GlcNAc transferases such as GlcNAcT-IV, GlcNAcT-V, and/or GlcNAcT-VI (Figure 188 and Figure 189) can also glycosylate the GlcNAc<sub>2</sub>Man<sub>3</sub>GlcNAc<sub>2</sub>-peptide. Additional glycosylation by the GalT 1 and sialyltransferases will form multi-antennary complex N-glycans. The enzyme GlcNAcT-III catalyzes the insertion of a bisecting GlcNAc, thus preventing the actions of ManII and subsequent action of transferases GlcNAcT-II, GlcNAcT-IV and GlcNAcT-V.

#### Tissue-Type Plasminogen Activator (TPA)

##### 39. Fucosylation of TPA to create Sialyl Lewis X

This example sets forth the preparation of Tissue Tissue-type Plasminogen Activator (TPA) with N-linked sialyl Lewis X antigen.

**Sialylation.** TPA expressed in mammalian cells will often contain a majority of the glycans terminating in sialic acid, but to ensure complete sialylation, it would be beneficial to first perform an *in vitro* sialylation. TPA in a suitable buffer (most preferably between pH 5.5 and 9, for example Tris buffered saline, pH 7.2) is incubated with CMP sialic acid and sialyltransferase for a time sufficient to convert any glycans lacking sialic acid to sialylated species. Typical conditions would be 1 mg/mL TPA, 3 mM CMP sialic acid, 0.02 U/mL ST3Gal3, 32°C for 24 hours. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. The TPA concentration is most preferably in the range 0.1 mg/mL up to the solubility limit of the peptide. The concentration of CMP-SA should be

sufficient for there to be excess over the available sites, and might range from 50  $\mu$ M up to 50 mM, and the temperature from 2°C up to 40°C. The time required for complete reaction will depend on the temperature, the relative amounts of enzyme to acceptor substrate, the donor substrate concentration, and the pH. Other sialyltransferases that may be capable of adding sialic acid in 2,3 linkage include ST3Gal4; microbial transferases could also be used.

**Fucosylation.** Typical conditions for fucosylation would be 1 mg/mL TPA, 3 mM GDP-fucose, 0.02 U/mL FTVI, 5 mM  $MnCl_2$ , 32°C for 24H in Tris buffered saline. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. The TPA concentration is most preferably in the range 0.1 mg/mL up to the solubility limit of the peptide. The concentration of GDP-fucose should be sufficient for there to be excess over the available sites, and might range from 50  $\mu$ M up to 50 mM, and the temperature from 2°C up to 40°C. The time required for complete reaction will depend on the temperature, the relative amounts of enzyme to acceptor substrate, the donor substrate concentration, and the pH. Other fucosyltransferases that may be capable of making sialyl Lewis x include FTVII, FTV, FTIII, as well as microbial transferases could also be used.

#### 40. Trimming of high mannose to tri-mannose core structure: Tissue-type Plasminogen Activator produced in CHO

This example sets forth the preparation of Tissue-type Plasminogen Activator with a trimannose core by trimming back from a high mannose glycan.

Tissue-type plasminogen activator (TPA) is currently produced in Chinese Hamster Ovary (CHO) cells and contains a low amount of high mannose N-linked oligosaccharide. The mannoses can be trimmed down using a variety of the specific mannosidases. The first step is to generate Man5GlcNAc2(Fuc0-1) from Man9GlcNAc2(Fuc0-1). This can be done using mannosidase I. Then either GlcNAcT1 (GlcNAc transferase I) is used to make GlcNAc1Man5GlcNAc2(Fuc0-1) or Mannosidase III is used to make Man3GlcNAc2(Fuc0-1). From Man3GlcNAc2(Fuc0-1), GlcNAc1Man3GlcNAc2(Fuc0-1) can be produced using GlcNAcT1 or from GlcNAc1Man5GlcNAc2(Fuc0-1), GlcNAc1Man3GlcNAc2(Fuc0-1) can be produced using Mannosidase II. GlcNAc1Man3GlcNAc2(Fuc0-1) is then converted into GlcNAc2Man3GlcNAc2(Fuc0-1) using GlcNAcTransferase II (GlcNAcTII). The two

terminal GlcNAc residues are then galactosylated using GalTI and then sialylated with SA-PEG using ST3GalIII.

Conversely, TPA can be produce in yeast or fungal systems. Similar processing would be required for fungal derived material.

5

#### 41. Generation and PEGylation of GlcNAc-Asn structures: TPA produced in Yeast

This example sets forth the preparation of PEGylated GlcNAc-Asn structures on a peptide such as TPA expressed in yeast.

10 Yeast expression is expected to result in a TPA which contains a single N-linked mannan-type structure. This recombinant glycoprotein is first treated with endoglycosidase H to generate GlcNAc structures on the asparagine (Asn) residues on the peptide.

The GlcNAc-Asn structures on the peptide/protein backbone are then be modified with galactose or galactose-PEG using UDP-galactose or UDP-galactose-6-PEG,  
15 respectively, and a galactosyltransferase such as GalT1. In one case, the galactose-PEG is the terminal residue. In the second case, the galactose is further modified with SA-PEG using a CMP-SA-PEG donor and a sialyltransferase such as ST3GalIII. In another embodiment, the GlcNAc-Asn structures on the peptide/protein backbone may be galactosylated and sialylated as described above, and then further sialylated using CMP-SA-  
20 PEG and an  $\alpha$ 2,8-sialyltransferase such as the enzyme encoded by the *Campylobacter jejuni* cst-II gene.

#### Transferrin

#### 42. GlycoPEGylation of Transferrin

25 This example sets forth the preparation of asialotransferrin and its sialylation with PEG-CMP-sialic acid.

**Preparation of Asialo-transferrin.** Human-derived holo-Transferrin, (10 mg) was dissolved in 500  $\mu$ L of 50 mM NaOAc, 5 mM CaCl<sub>2</sub>, pH 5.5. To this solution was added 500 mU Neuraminidase II (*Vibrio cholerae*) and the reaction mixture was shaken gently for  
30 20.5 hours at 37 °C. The reaction mixture was added to the prewashed N-(p-aminophenyl)oxamic acid-agarose conjugate (600  $\mu$ L) and the washed beads gently rotated

for 24 hours at 4 °C. The mixture was centrifuged at 10,000 rpm and the supernatant was collected. The reaction mixture was adjusted to 5 mM EDTA by addition of 100 µL of 30 mM EDTA to the washed beads, which were gently rotated for 20 hours at 4 °C. The suspension was centrifuged for 2 minutes at 10,000 rpm and the supernatant was collected.

- 5 The beads were washed 5 times with 0.35 mL of 50 mM NaOAc, 5 mM CaCl<sub>2</sub>, 5 mM EDTA, pH 5.5 and all supernatants were pooled. The enzyme solution was dialyzed twice at 4 °C into 15 mM Tris-HCl, 1 M NaCl, pH 7.4. 0.3 mL of the transferrin solution (3.3 mL total) was removed and dialyzed twice against water. The remainder was dialyzed twice more at 4 °C against phosphate buffered saline. The dialyzed solution was stored at -20 °C.
- 10 Protein samples were analyzed by IEF Electrophoresis. Samples (9 µL, 25 µg) were diluted with 16 µL Tris buffer and mixed with 25 µL of the sample loading buffer and applied to Isoelectric Focusing Gels (pH 3-7). Gels were run and fixed using standard procedures. Gels were stained with Colloidal Blue Stain.

- Sialyl-PEGylation of asialo-Transferrin.** Desialylated transferrin (250 µg) and
- 15 CMP-sialic acid or CMP-SA-PEG (1 kDa or 10 kDa)(0.05 µmol) were dissolved in 69 µL 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2 in 1.5 mL plastic tubes. The tubes were vortexed briefly and 100 mU ST3Gal3 (90 µL) were added (total volume 250 µL). The tubes were vortexed again and mixed gently for 24 hours at 32 °C. The reactions were stopped by freezing at -80 °C. Novex Tris-Glycine 8-16% 1 mm gels were used for SDS
- 20 PAGE analysis (Figure 190). Samples (25 µL, 25 µg) were mixed with 25 µL of sample loading buffer and 0.4 µL of β-mercaptoethanol and heated for 6 minutes at 85 °C. Gels were run using standard conditions and stained with Colloidal Blue Stain. IEF gels were also performed as described above (Figure 191). Samples were also dialyzed against water analyzed by MALDI-TOF.

- 25 **Results.** MALDI was also performed. Native transferrin (78729); asialotransferrin (78197); resialylated transferrin (79626/80703); with SA-PEG 1k (79037 (1); 80961 (2); 82535 (3); 84778 (4)); with SA-PEG 5k (90003 (2); 96117 (3); 96117 (4)); with SA-PEG 10k (100336 (2); 111421 (3); 122510 (4)).

### 43. Transferrin-GDNF

This example sets forth the procedures for the glycoconjugation of proteins, and in particular, transferrin is glycoconjugated to GDNF. Transferrin-SA-Linker-Gal-UDP is prepared from transferrin. The galactose residue is removed from GDNF glycans, and  
5 Transferrin-SA-Linker-Gal-UDP is conjugated to GDNF glycans using a galactosyltransferase.

**Preparation of agalacto-GDNF.** GDNF produced in NSO cells (NSO murine myeloma cells) is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, and is incubated with 300 mU/mL beta-galactosidase-agarose conjugate for 16 hours at  
10 32°C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel performed according to Invitrogen procedures. The mixture is centrifuged at 10,000 rpm and the supernatant is collected. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub> and then twice more against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN<sub>3</sub>. The dialyzed solution is then concentrated  
15 using a Centricon Plus 20 centrifugal filter and stored at -20 °C. The conditions for the IEF gel are run according to the procedures and reagents provided by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of Transferrin-SA-Linker-Gal-UDP.** Asialo-transferrin is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is  
20 incubated with CMP-sialic acid-linker-Gal-UDP (molar amount to add 1 molar equivalent of nucleotide sugar to transferrin) and 0.1 U/mL of ST3Gal3 at 32°C for 2 days. To monitor the incorporation of sialic acid, a small aliquot of the reaction has <sup>14</sup>C-SA-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label  
25 incorporation into the peptide is quantitated using an in-line radiation detector.

The solution is incubated with 5 mM CMP-sialic acid and 0.1 U/mL of ST3Gal3 (to cap any unreacted transferrin glycans) at 32°C for 2 days. The incorporation into the peptide is quantitated using an in-line UV detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting  
30 fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE

and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

**Preparation of Transferrin-SA-Linker-Gal-GDNF.** The transferrin-SA-Linker-Gal-UDP prepared as described above is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl<sub>2</sub>, 0.05% NaN<sub>3</sub>, pH 7.2. The solution is incubated with 2.5 mg/mL agalacto-GDNF and 0.1 U/mL of galactosyltransferase at 32°C for 2 days. To monitor the incorporation of galactose, a small aliquot of the reaction has <sup>14</sup>C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

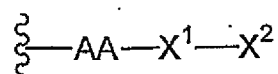
When the reaction is complete, the solution is incubated with 5 mM UDP-Gal and 0.1 U/mL of galactosyltransferase (to cap any unreacted transferrin glycans) at 32°C for 2 days followed by addition of 5 mM CMP-SA and 0.1 U/mL of ST3Gal3. After 2 additional days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety.

While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

What is claimed:

1. A cell-free, in vitro method of remodeling a peptide comprising poly(ethylene glycol), the peptide having the formula:



wherein

AA is a terminal or internal amino acid residue of the peptide;

$\text{X}^1 - \text{X}^2$  is a saccharide covalently linked to the AA, wherein

$\text{X}^1$  is a first glycosyl residue; and

$\text{X}^2$  is a second glycosyl residue covalently linked to  $\text{X}^1$ , wherein  $\text{X}^1$  and  $\text{X}^2$  are

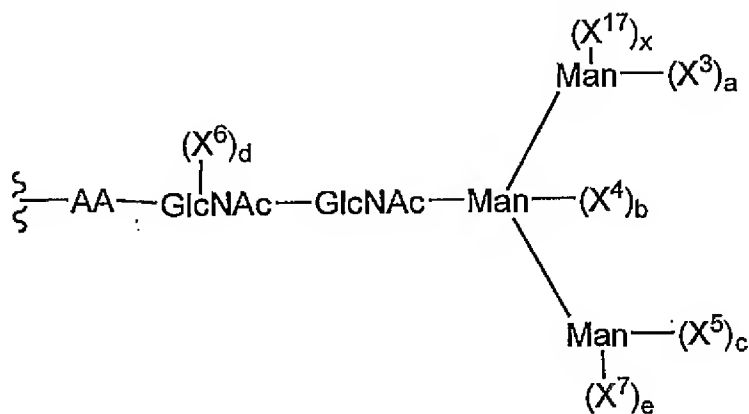
selected from monosaccharyl and oligosaccharyl residues;

the method comprising:

(a) removing  $\text{X}^2$  or a saccharyl subunit thereof from the peptide, thereby forming a truncated glycan.

2. The method according to claim 1 wherein said truncated glycan is formed by removing a Sia residue.

3. The method according to claim 1 wherein said peptide has the formula:



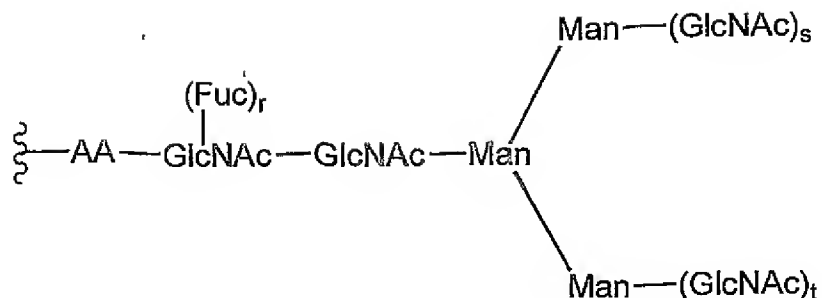
wherein



$X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$ , and  $X^{17}$ , are independently selected monosaccharyl or oligosaccharyl residues; and

a, b, c, d, e, and x are independently selected from the integers 0, 1 and 2.

- 5                   4.     The method according to claim 3 wherein said oligosaccharyl residue is a member selected from GlcNAc-Gal-Sia and GlcNAc-Gal.
5.     The method according to claim 3 wherein at least one member selected from a, b, c, d, e and x is 1 or 2.
- 10               6.     The method of claim 3, wherein said removing of step (a) produces a truncated glycan in which at least one of a, b, c, e and x are 0.
7.     The method of claim 6, wherein  $X^3$ ,  $X^5$  and  $X^7$  are members
- 15               independently selected from (mannose)<sub>z</sub> and (mannose)<sub>z</sub>-( $X^8$ )  
                   wherein  
                    $X^8$  is a glycosyl moiety selected from mono- and oligo-saccharides; and  
                   z is an integer between 1 and 20, wherein  
                   when z is 3 or greater, each (mannose)<sub>z</sub> is independently selected from linear  
- 20     and branched structures.
- 8.     The method of claim 6 wherein  $X^4$  is selected from the group consisting of GlcNAc and xylose.
- 25               9.     The method of claim 6, wherein  $X^3$ ,  $X^5$  and  $X^7$  are (mannose)<sub>u</sub>  
                   wherein  
                   u is selected from the integers between 1 and 20, and when u is 3 or greater,  
                   each (mannose)<sub>u</sub> is independently selected from linear and branched structures.
- 30               10.    The method according to claim 3 wherein said peptide has the formula:

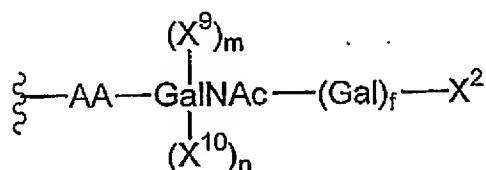


wherein

r, s, and t are integers independently selected from 0 and 1.

5

11. The method of claim 1, wherein said peptide has the formula:



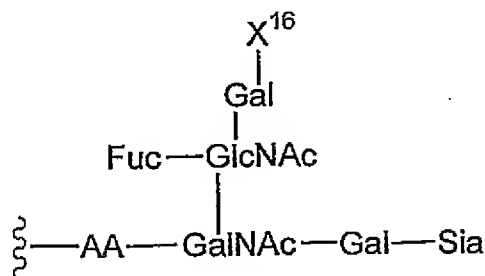
wherein

X<sup>9</sup> and X<sup>10</sup> are independently selected monosaccharyl or oligosaccharyl

10 residues; and

m, n and f are integers independently selected from 0 and 1.

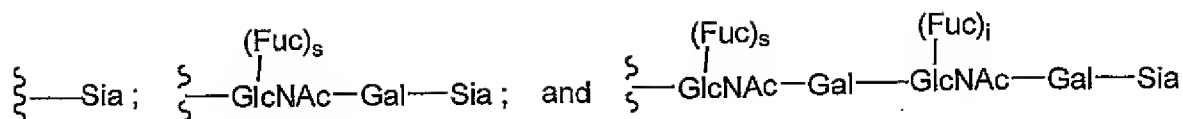
12. The method of claim 11, wherein said peptide has the formula:



15

wherein

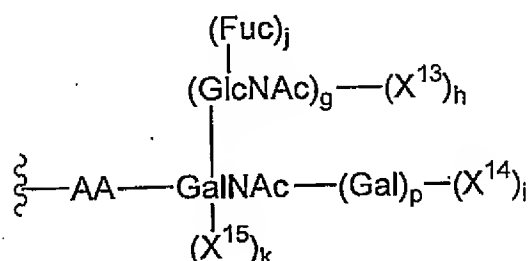
X<sup>16</sup> is a member selected from:



wherein

s and i are integers independently selected from 0 and 1.

5                    13.    The method of claim 12, wherein said peptide has the formula:



wherein

$\text{X}^{13}$ ,  $\text{X}^{14}$ , and  $\text{X}^{15}$  are independently selected glycosyl residues; and  
g, h, i, j, k, and p are independently selected from the integers 0 and 1

10

14.    The method according to claim 13 wherein at least one of g, h, i, j, k  
and p is 1.

15

15.    The method of claim 13, wherein  
 $\text{X}^{14}$  and  $\text{X}^{15}$  are members independently selected from GlcNAc and Sia; and  
i and k are independently selected from the integers 0 and 1.

16.    The method according to claim 15 wherein at least one of i and k is 1,  
and if k is 1, g, h, and j are 0.

20

17.    The method according to claim 1, further comprising:

(b)    contacting the truncated glycan with at least one glycosyltransferase  
and at least one glycosyl donor under conditions suitable to transfer the at least one glycosyl

donor to the truncated glycan, thereby remodeling said peptide comprising poly(ethylene glycol).

18. The method according to claim 17 wherein said glycosyl donor  
5 comprises a modifying group covalently linked thereto.

19. The method of claim 1, further comprising:

(c) removing  $X^1$ , thereby exposing AA.

10 20. The method according to claim 19, further comprising:

(d) contacting AA with at least one glycosyltransferase and at least one glycosyl donor under conditions suitable to transfer said at least one glycosyl donor to AA, thereby remodeling said peptide comprising poly(ethylene glycol).

15 21. The method according to claim 20 wherein said at least one glycosyl donor comprises a modifying group covalently linked thereto.

22. The method according to claim 21 wherein said modifying group is poly(ethylene glycol).

20

23. The method according to claim 22 wherein said poly(ethylene glycol) has a molecular weight distribution that is essentially homodisperse.

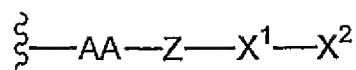
24. The method of claim 17, further comprising:

25 (e) prior to step (b), removing a group added to said saccharide during post-translational modification.

25. The method of claim 24 wherein said group is a member selected from phosphate, sulfate, carboxylate and esters thereof.

30

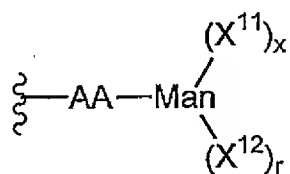
26. The method of claim 1 wherein said peptide has the formula:



wherein

Z is a member selected from O, S, NH and a cross-linker.

- 5                    27.    The method of claim 1, wherein said peptide has the formula:



wherein

$\text{X}^{11}$  and  $\text{X}^{12}$  are independently selected glycosyl moieties; and

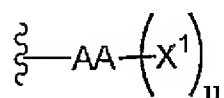
r and x are integers independently selected from 0 and 1.

10

28.    The method of claim 27, wherein  $\text{X}^{11}$  and  $\text{X}^{12}$  are  $(\text{mannose})_q$ , wherein q is selected from the integers between 1 and 20, and when q is three or greater,  $(\text{mannose})_q$  is selected from linear and branched structures.

- 15                    29.    A pharmaceutical composition comprising a pharmaceutically acceptable diluent and a remodeled peptide according to claim 1.

30.    A cell-free, in vitro method of remodeling a peptide comprising poly(ethylene glycol), said peptide having the formula:



20

wherein

AA is a terminal or internal amino acid residue of said peptide;  
X<sup>1</sup> is a glycosyl residue covalently linked to said AA, selected from  
monosaccharyl and oligosaccharyl residues; and  
u is an integer selected from 0 and 1,

5       said method comprising:

contacting said peptide with at least one glycosyltransferase and at least one  
glycosyl donor under conditions suitable to transfer said at least one glycosyl donor to said  
truncated glycan, thereby remodeling said peptide.

10               31.    The method according to claim 30 wherein said at least one glycosyl  
donor comprises a modifying group covalently linked thereto.

                  32.    The method according to claim 30 wherein said modifying group is  
poly(ethylene glycol).

15               33.    The method according to claim 32 wherein said poly(ethylene glycol)  
has a molecular weight distribution that is essentially homodisperse.

                  34.    A pharmaceutical composition comprising a pharmaceutically  
20   acceptable diluent and a remodeled peptide according to claim 30.

1/497

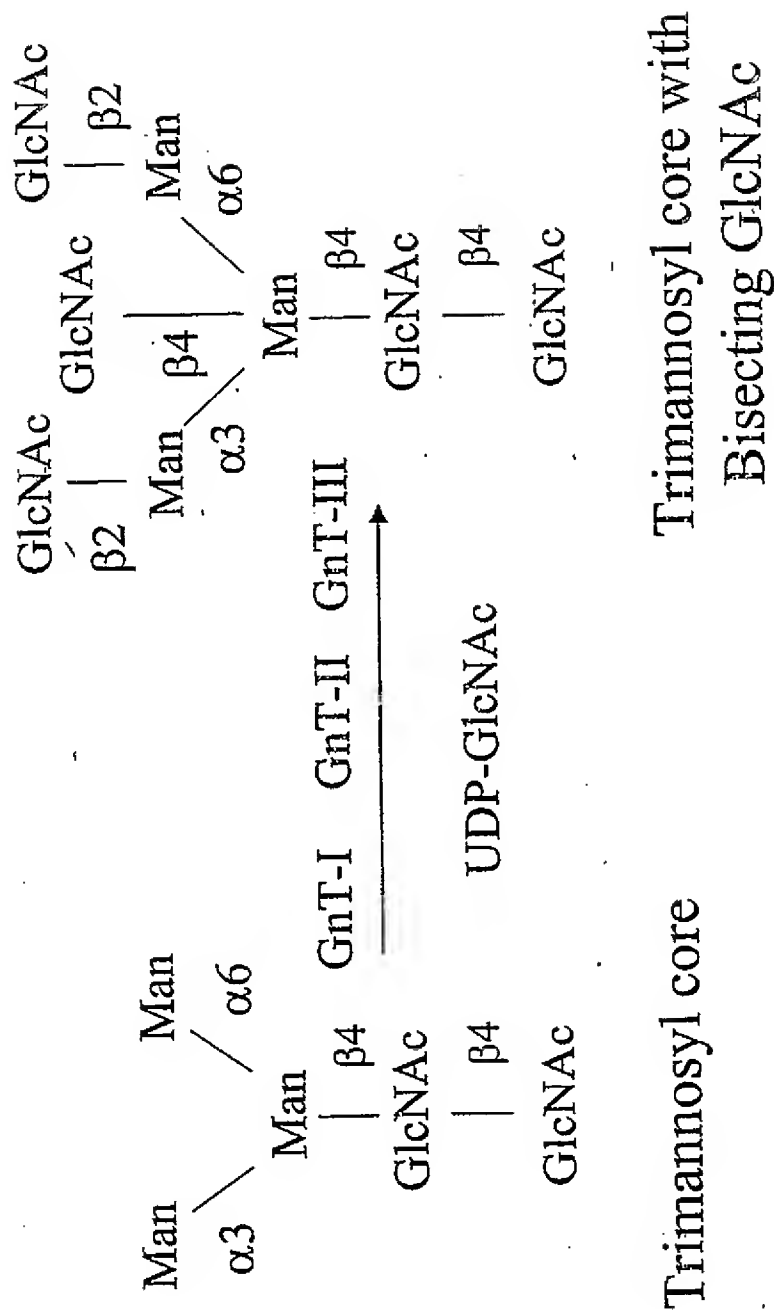


FIG. 1

2/497

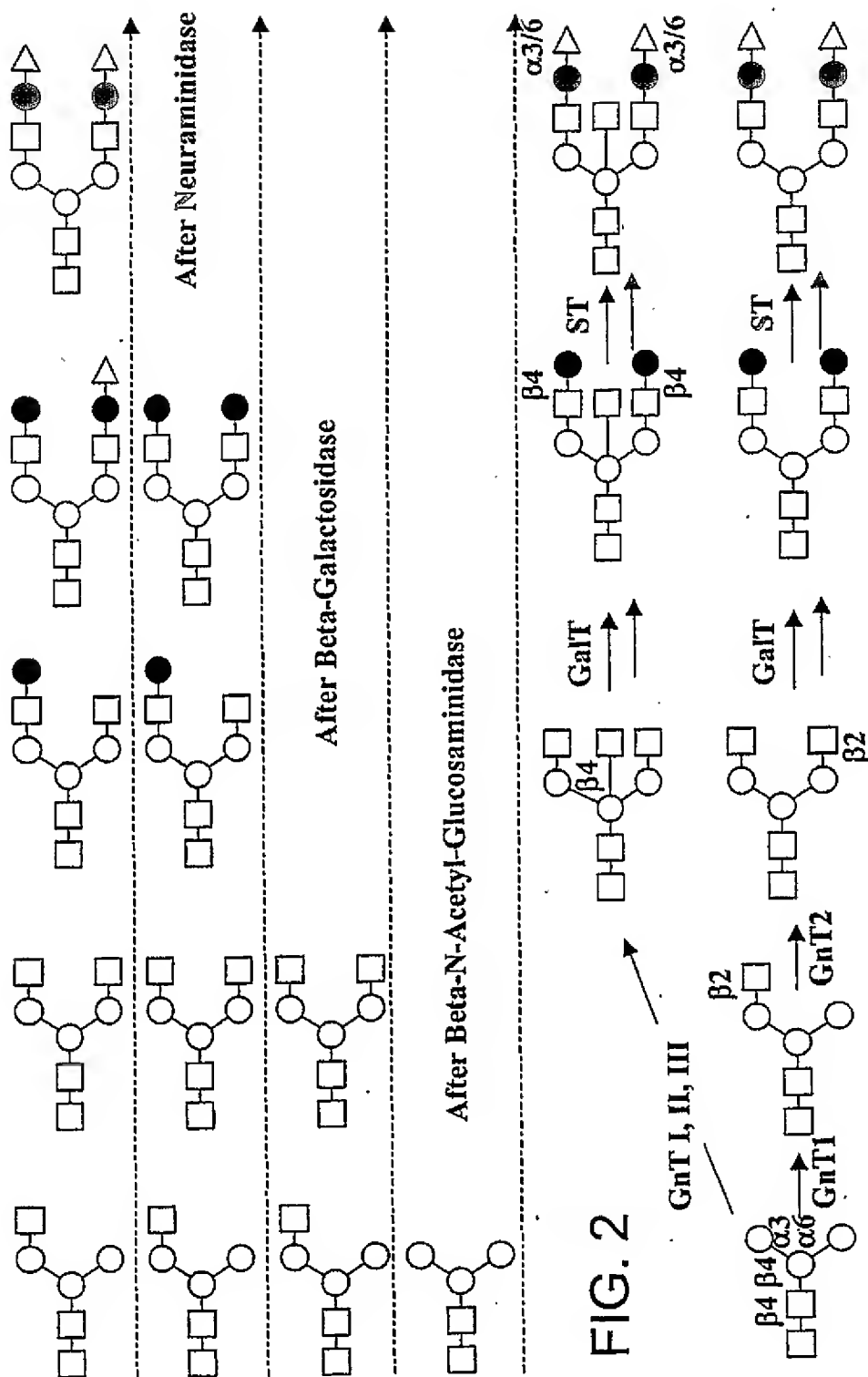


FIG. 2



3/497

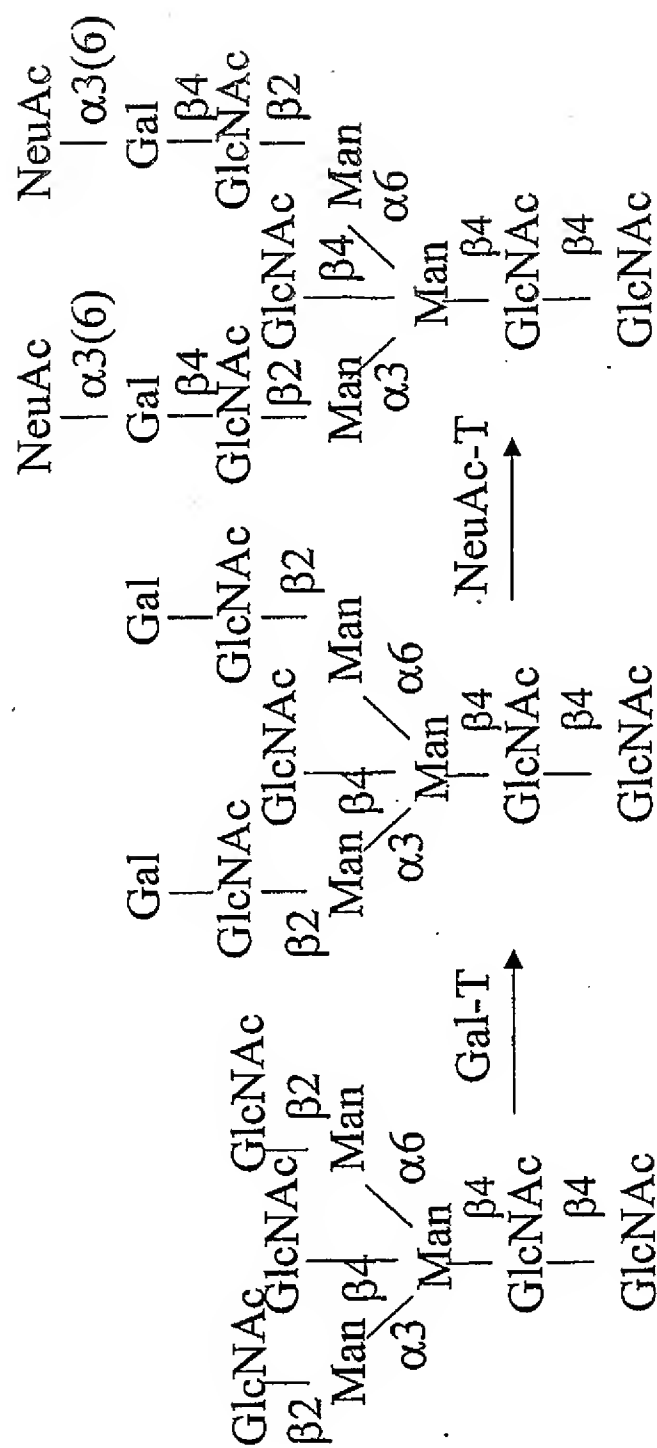


FIG. 3

4/497

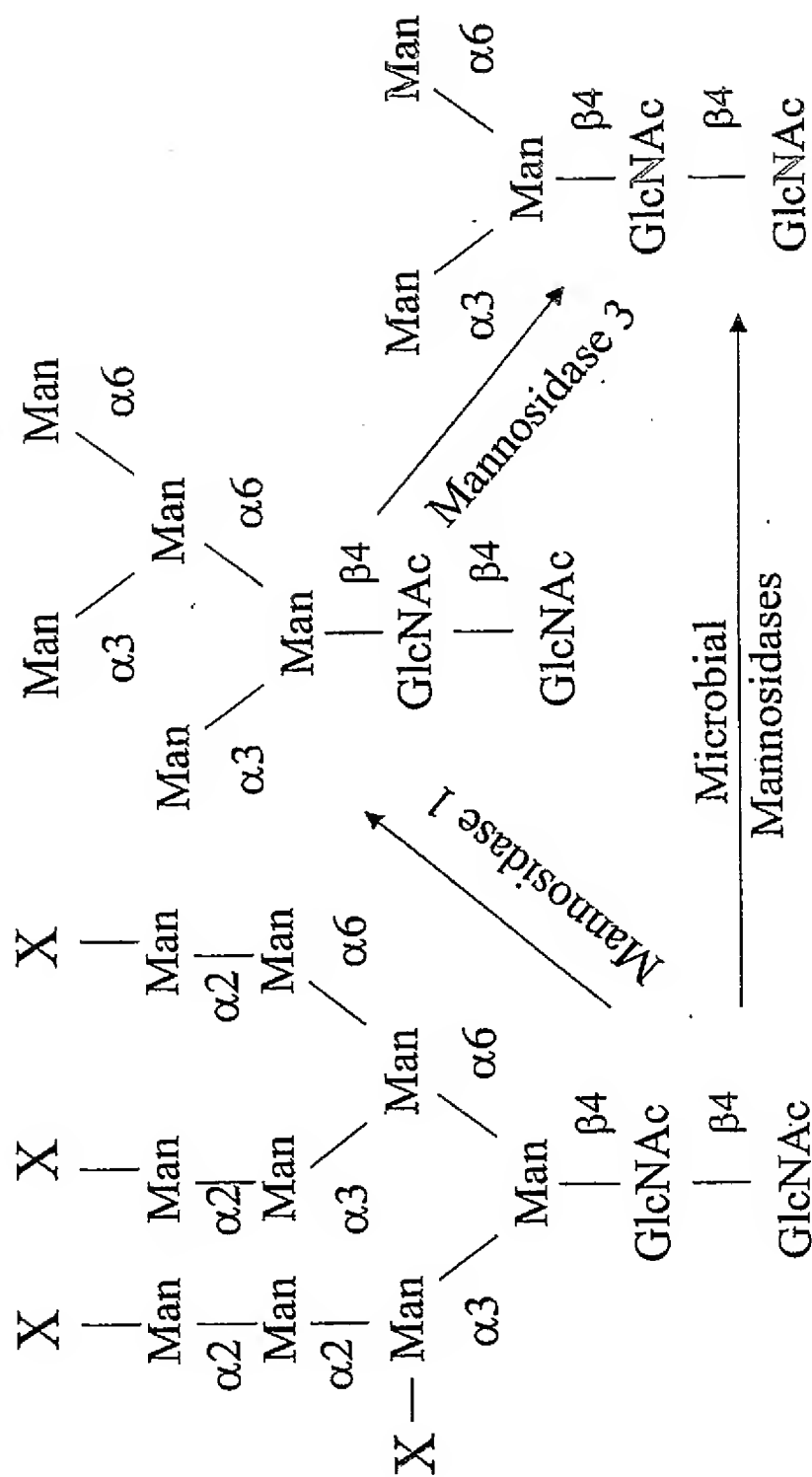


FIG. 4

5/497

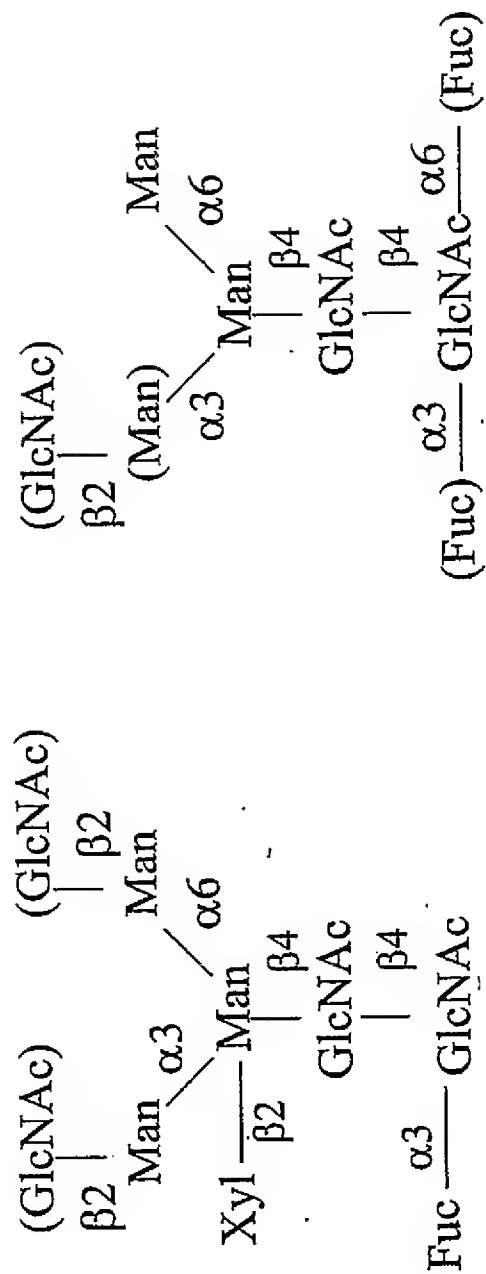


FIG. 6

FIG. 5

6/497

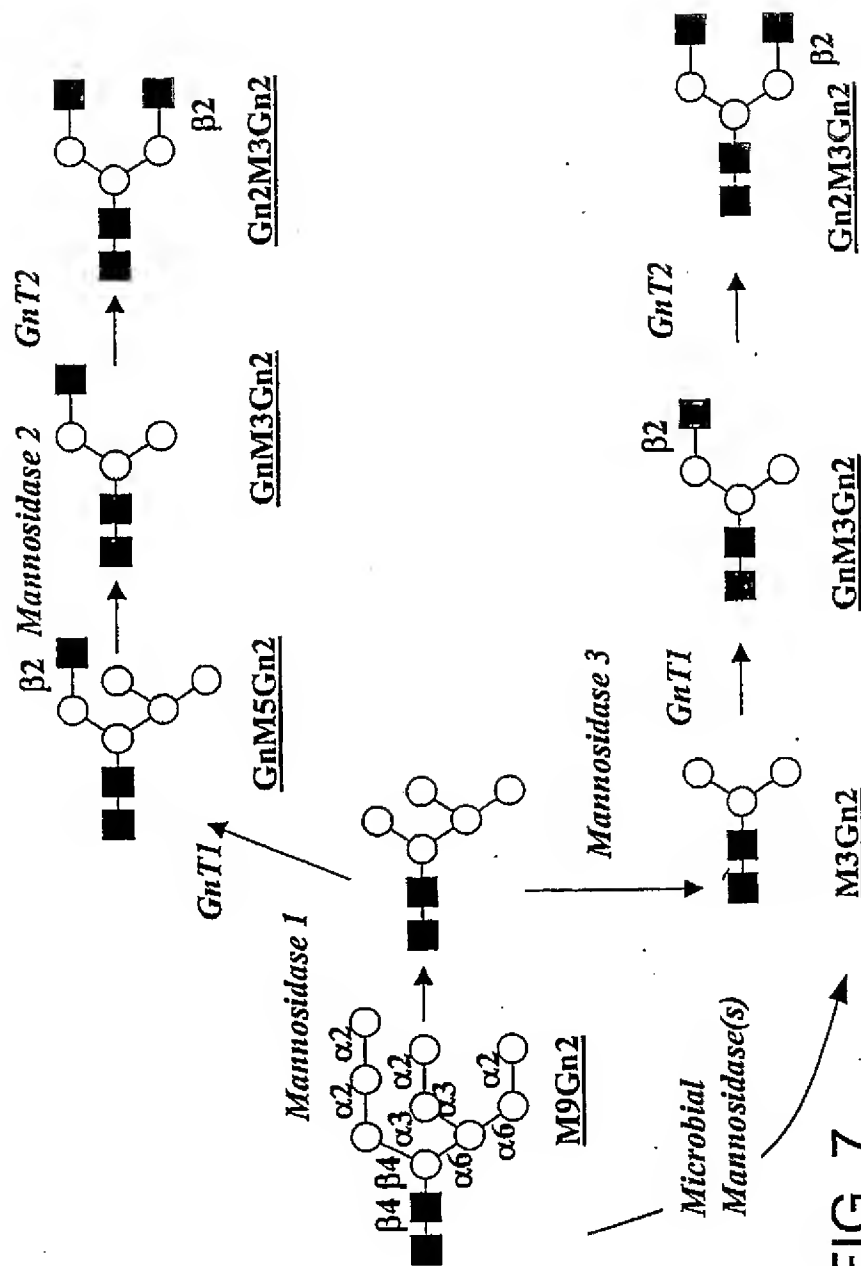


FIG. 7

7/497

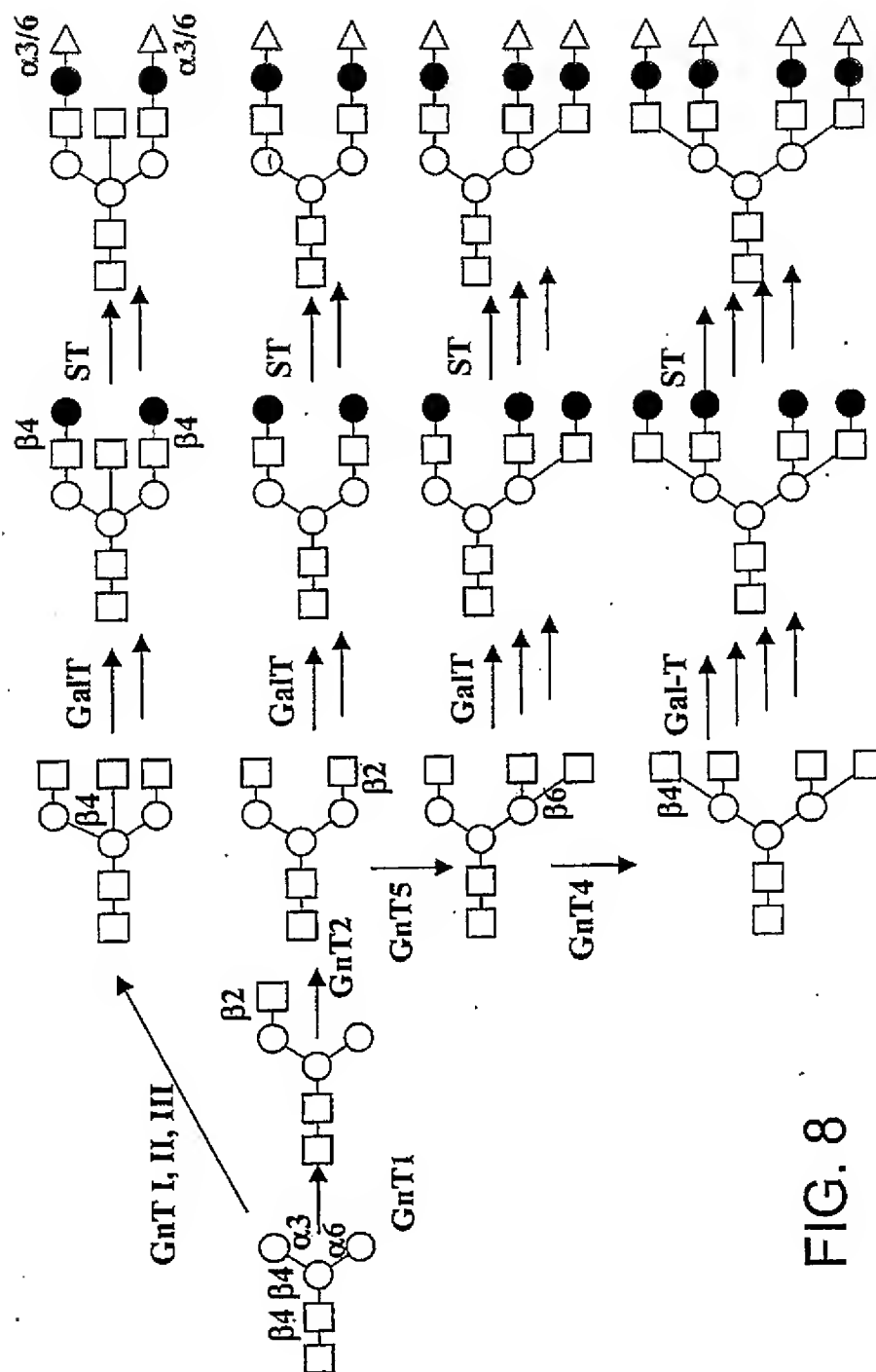


FIG. 8

8/497

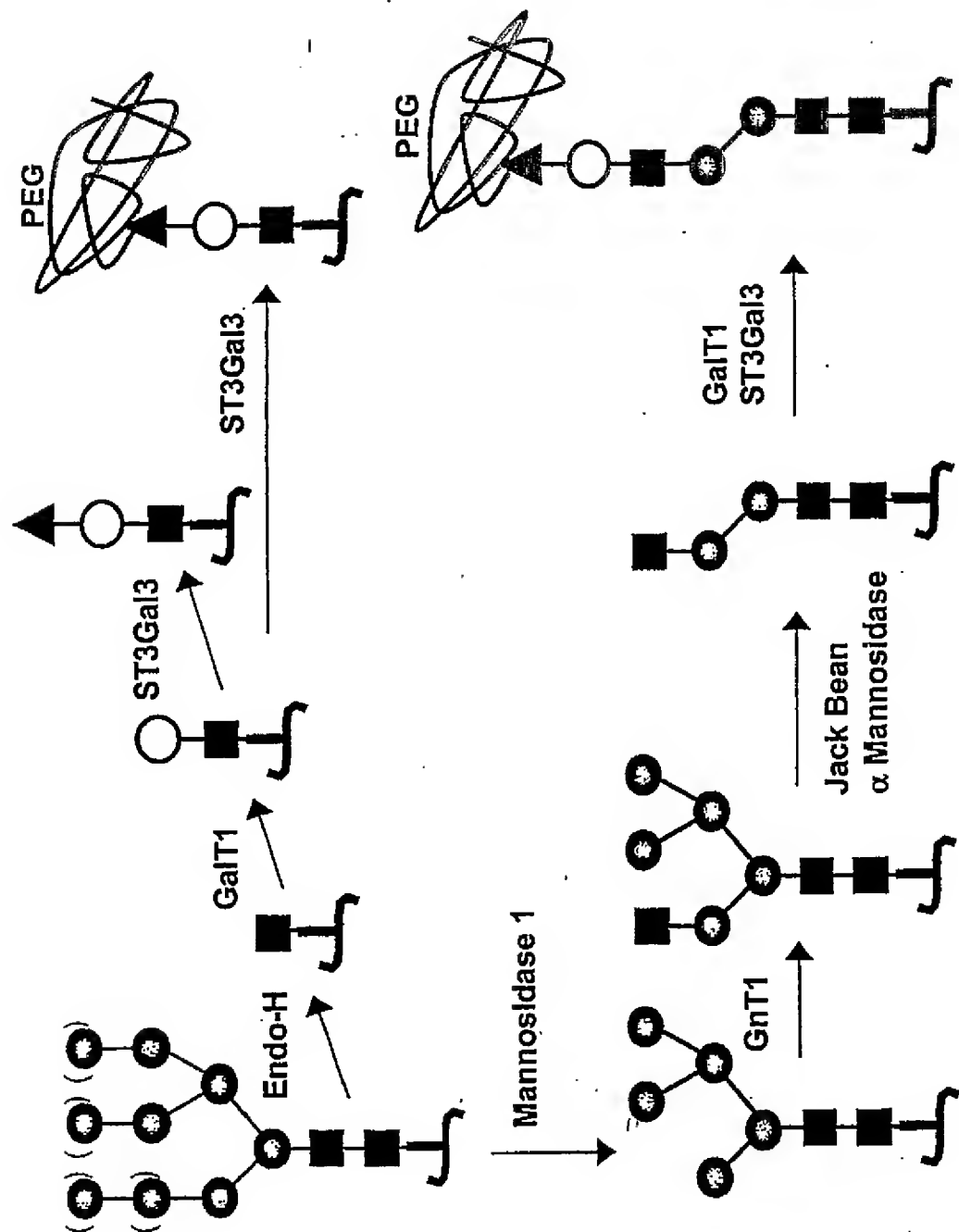
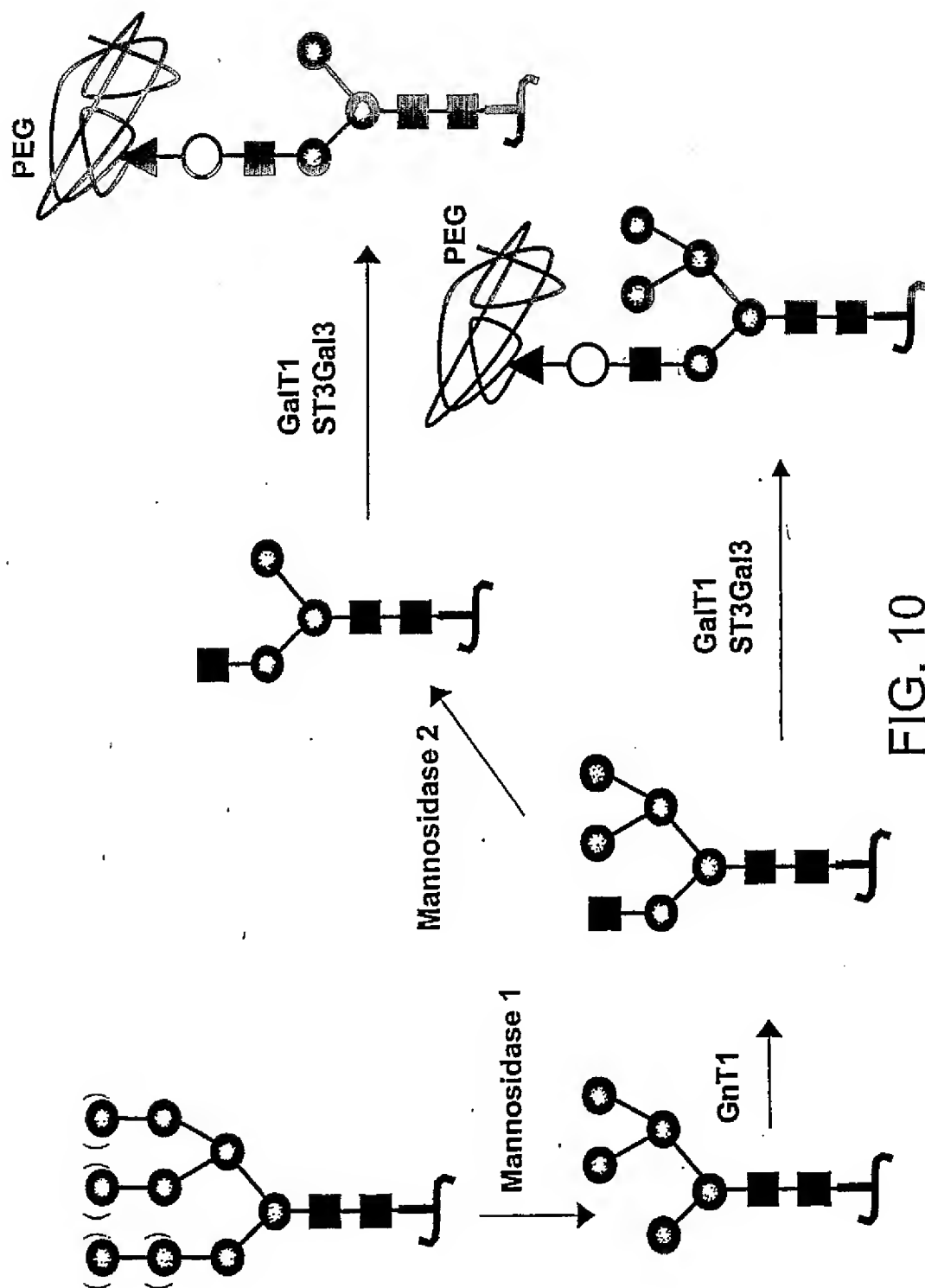


FIG. 9

9/497



10/497

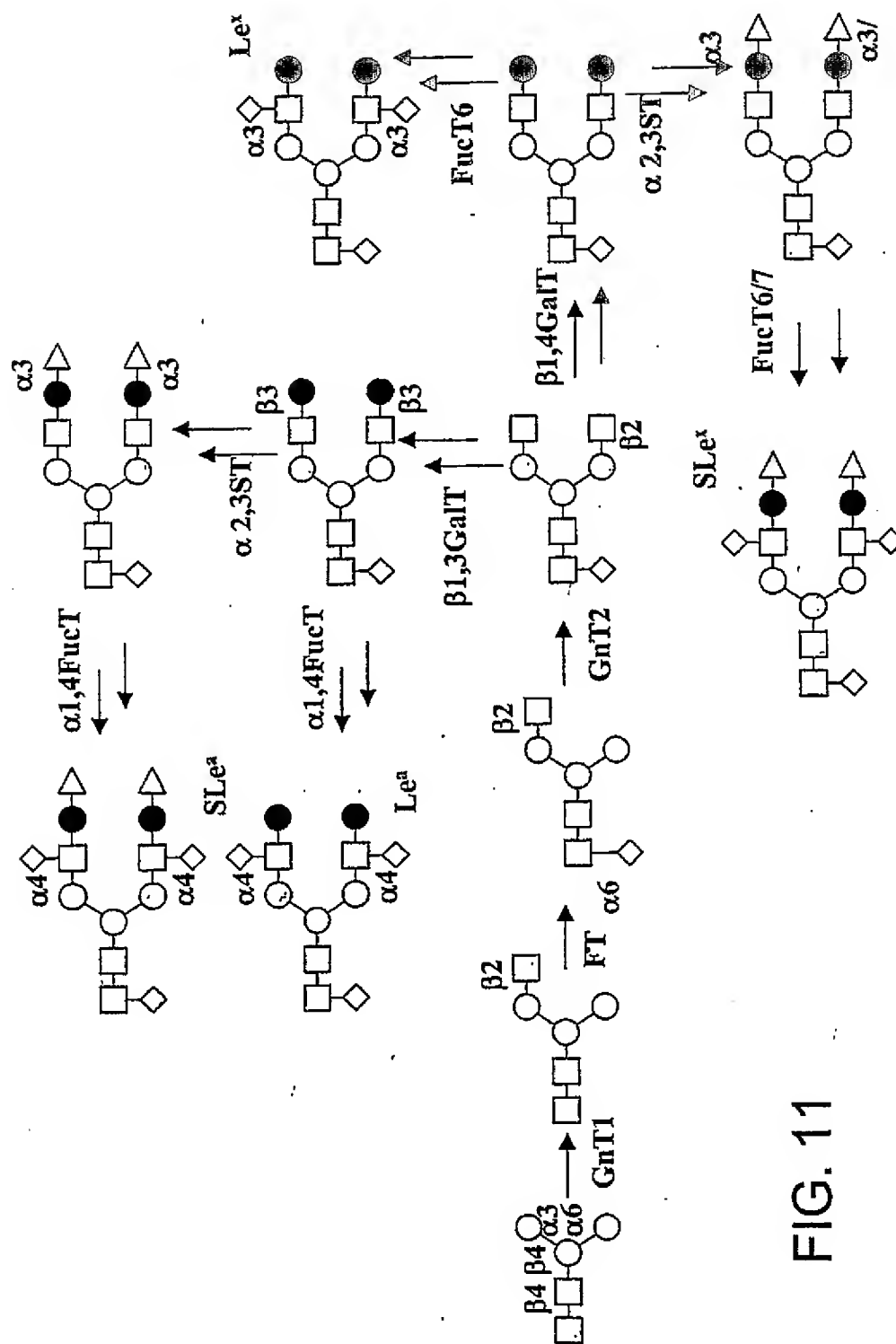


FIG. 11



11/497

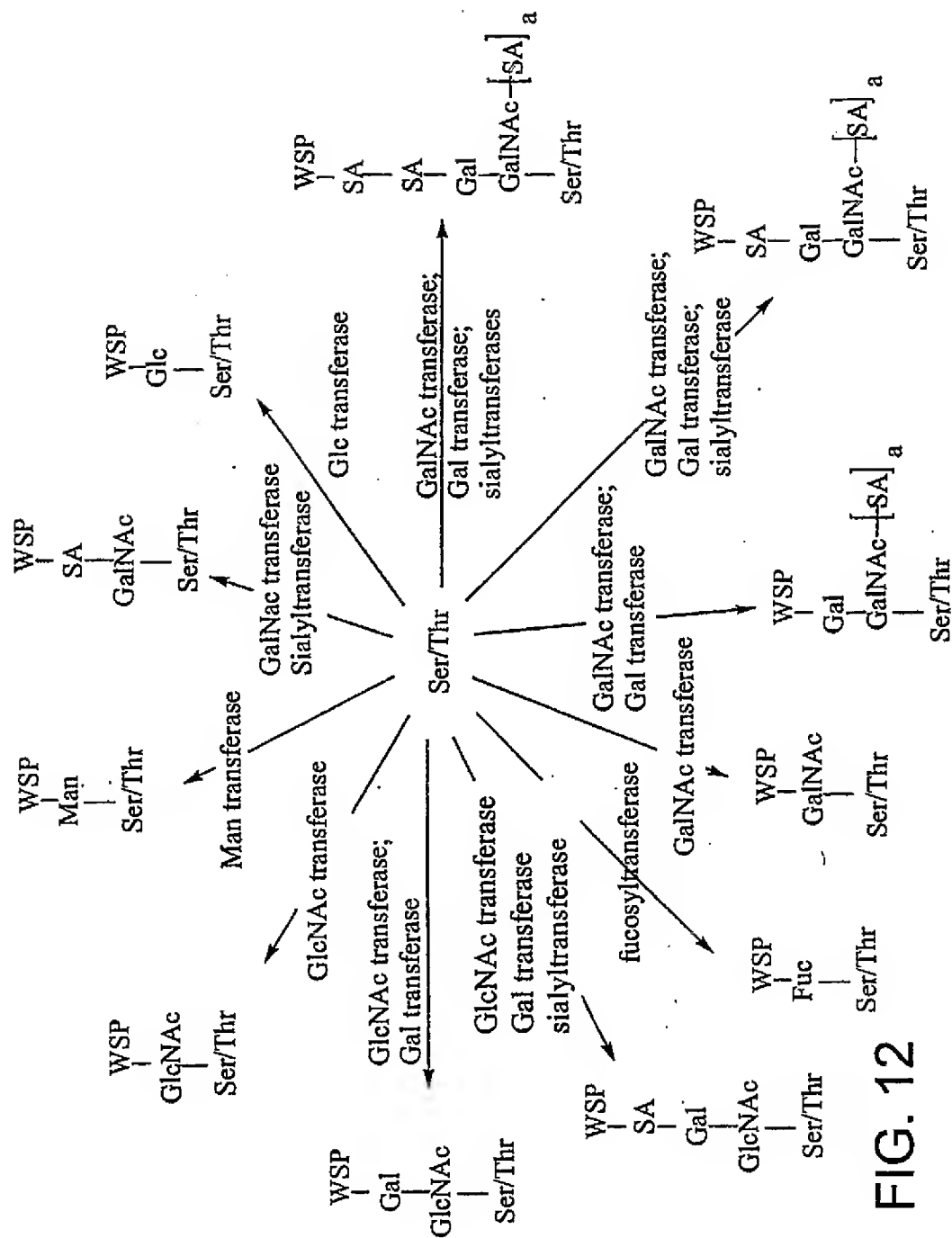


FIG. 12

12/497

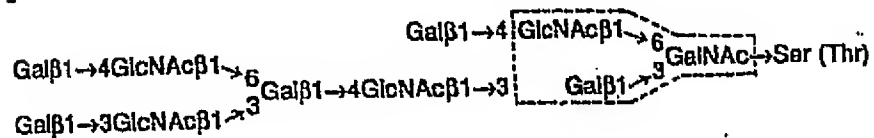
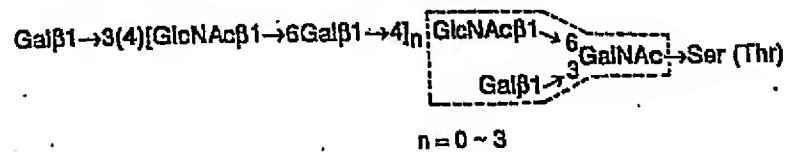
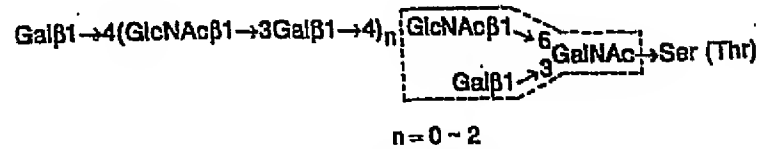
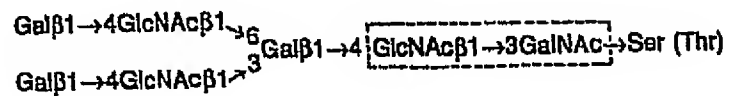
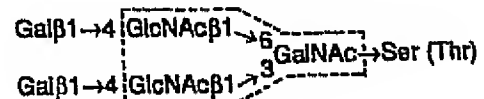
*Core 1**Core 2**Core 3**Core 4*

FIG. 13



14/497

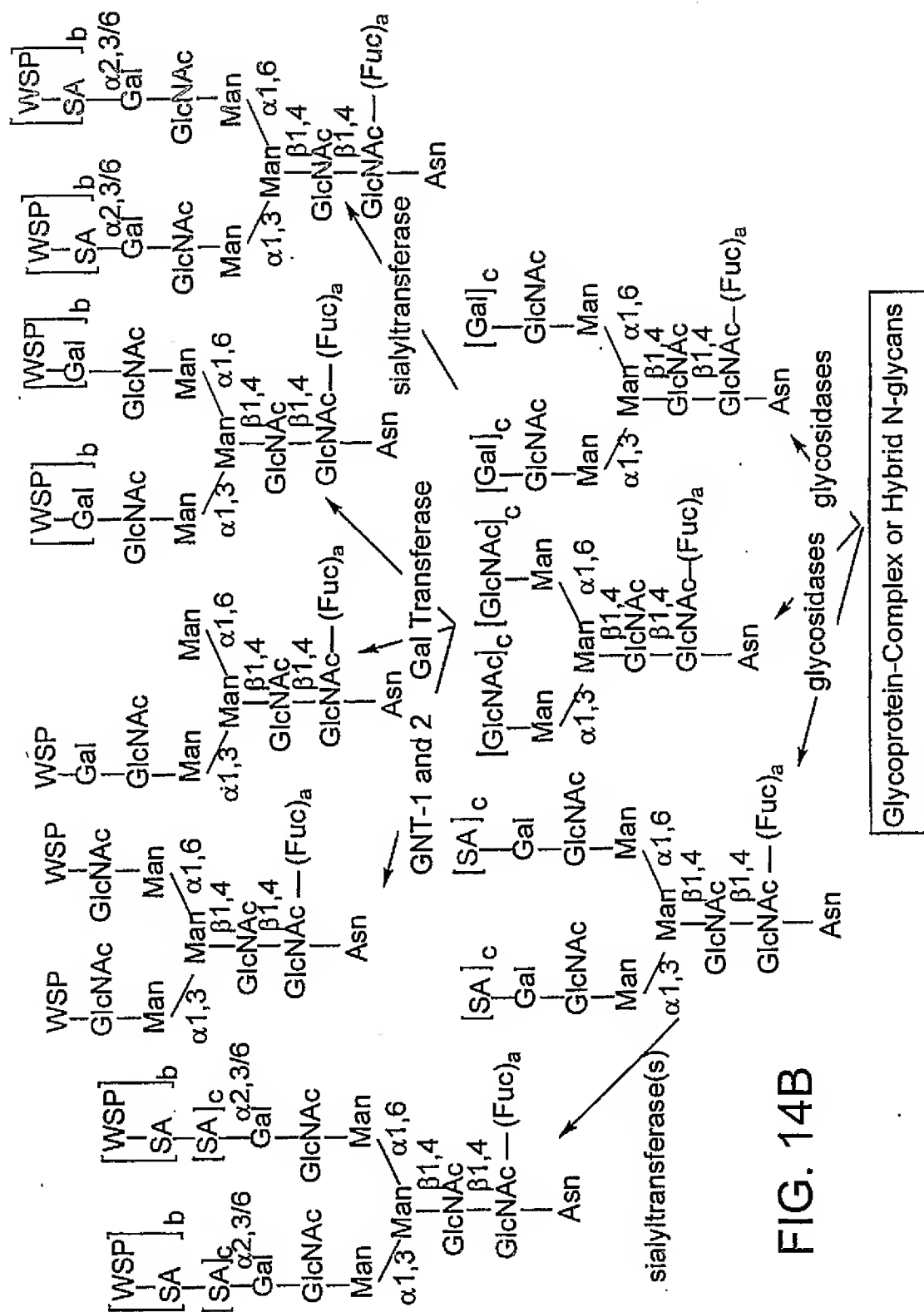


FIG. 14B

15/497

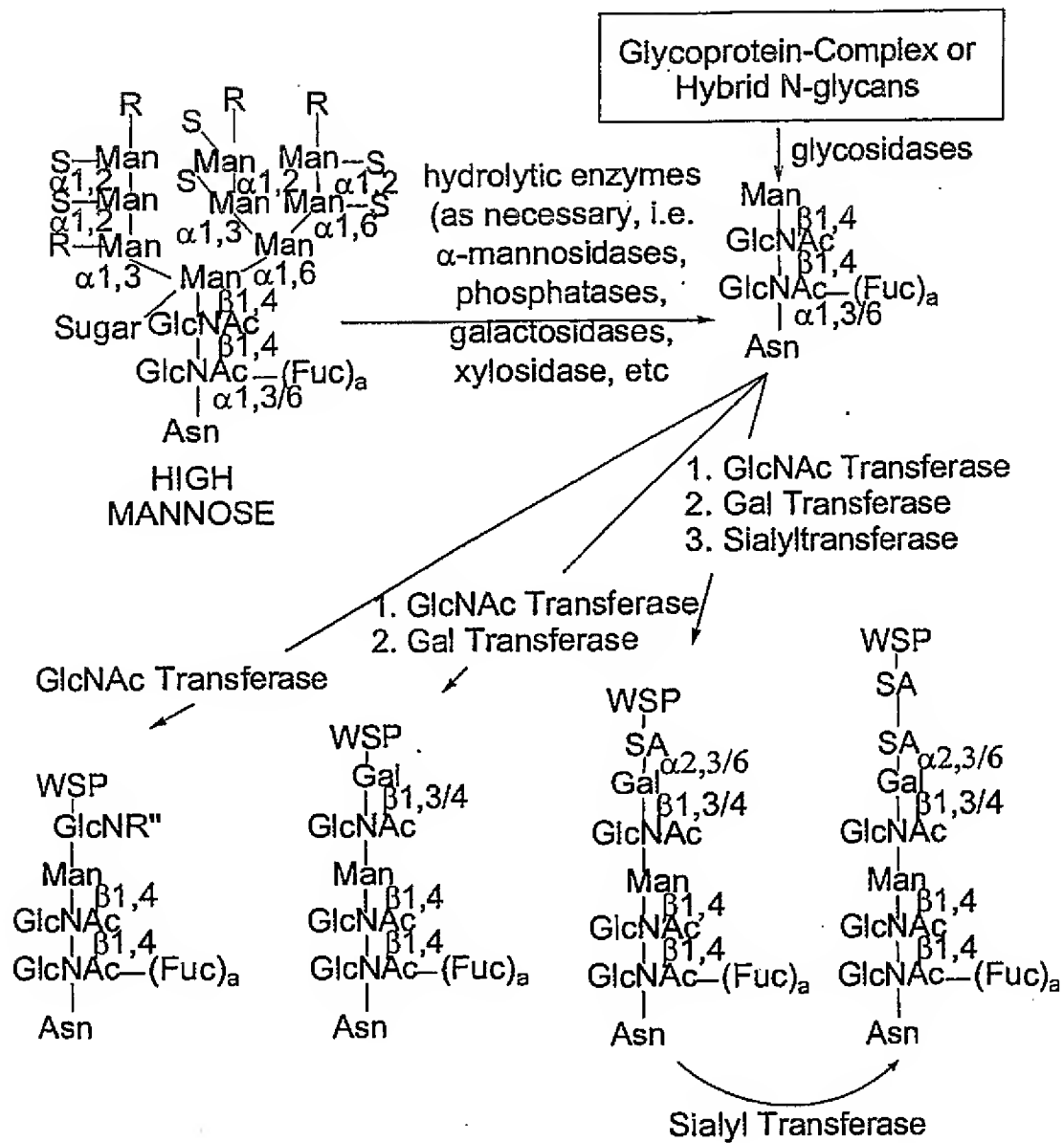


FIG. 15

16/497

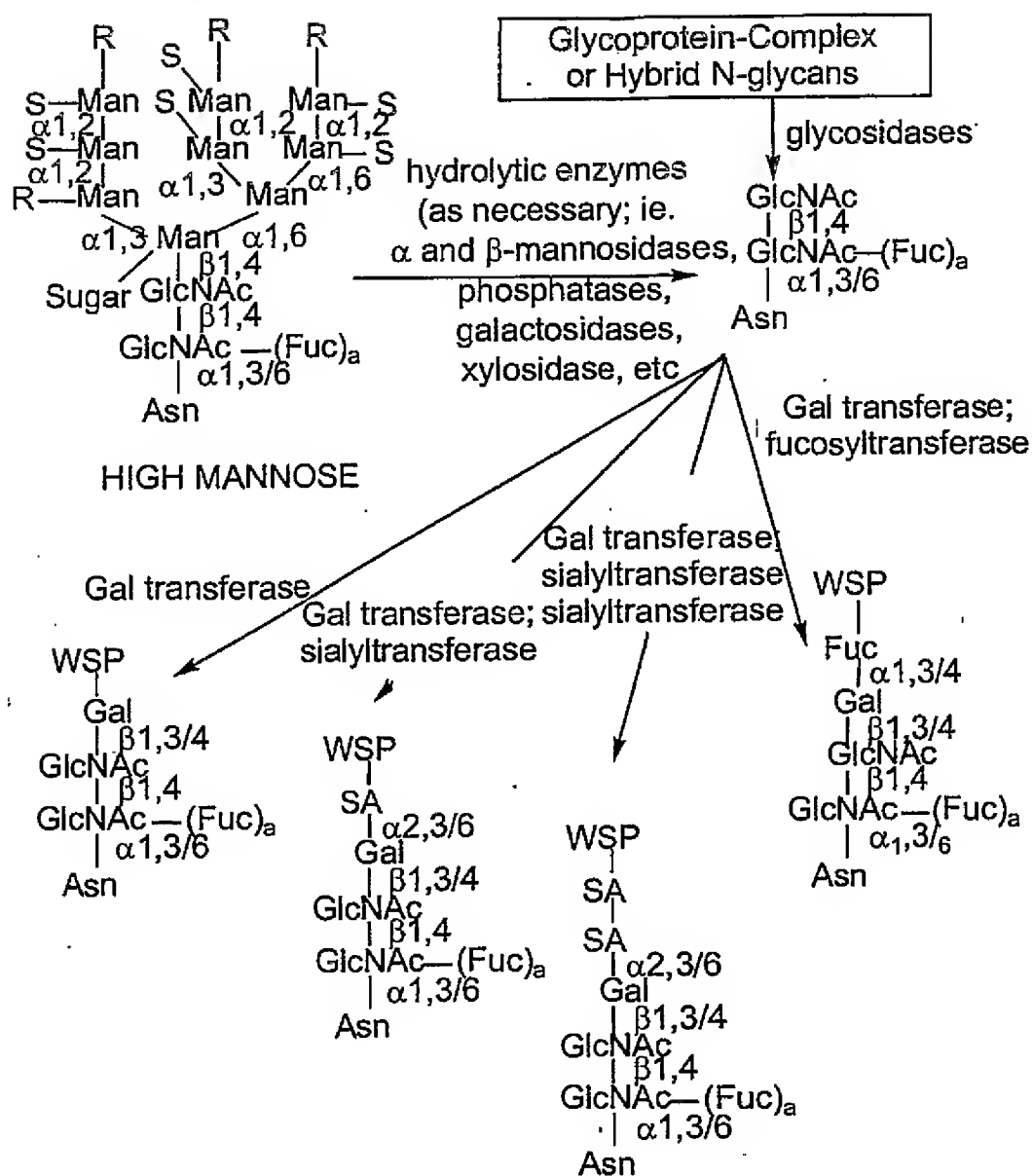


FIG. 16

17/497

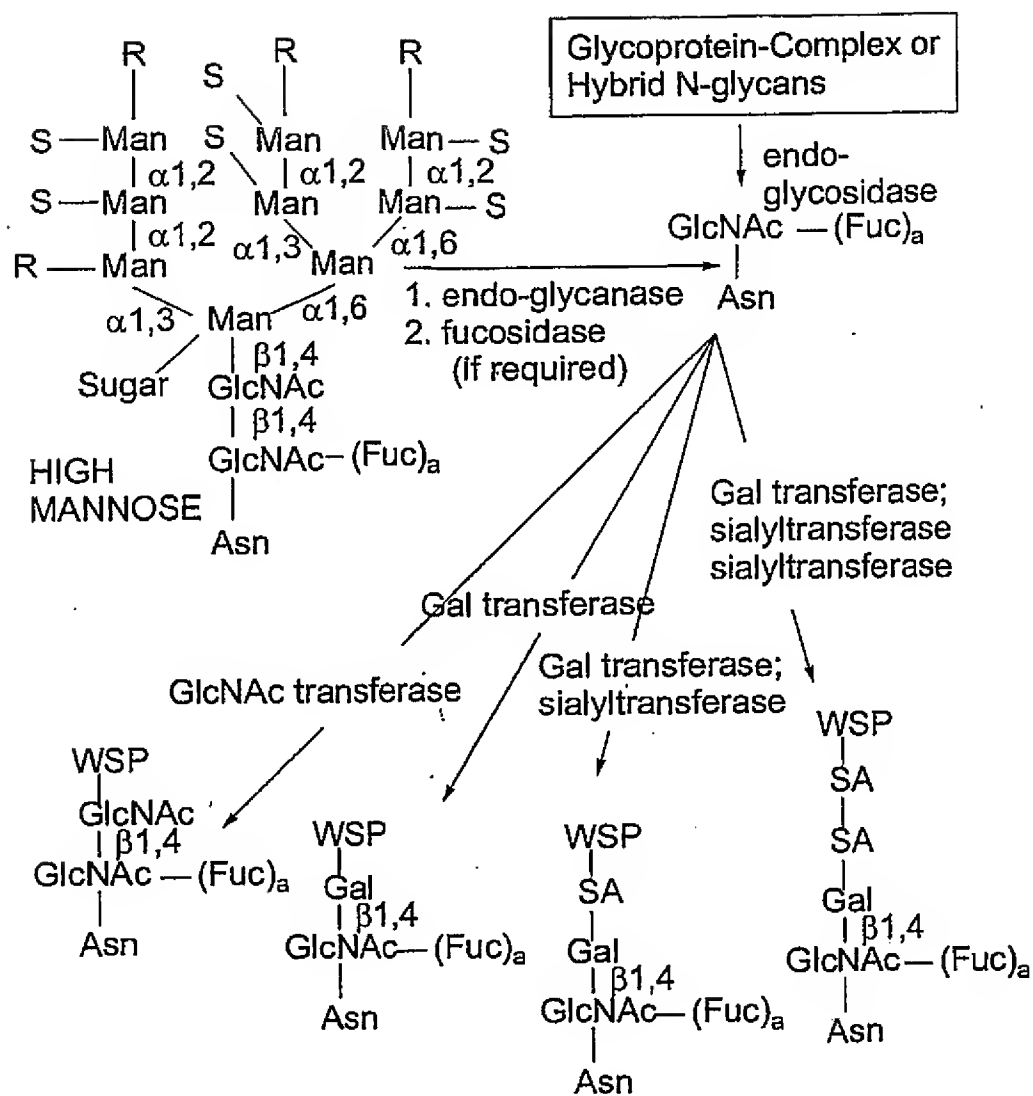
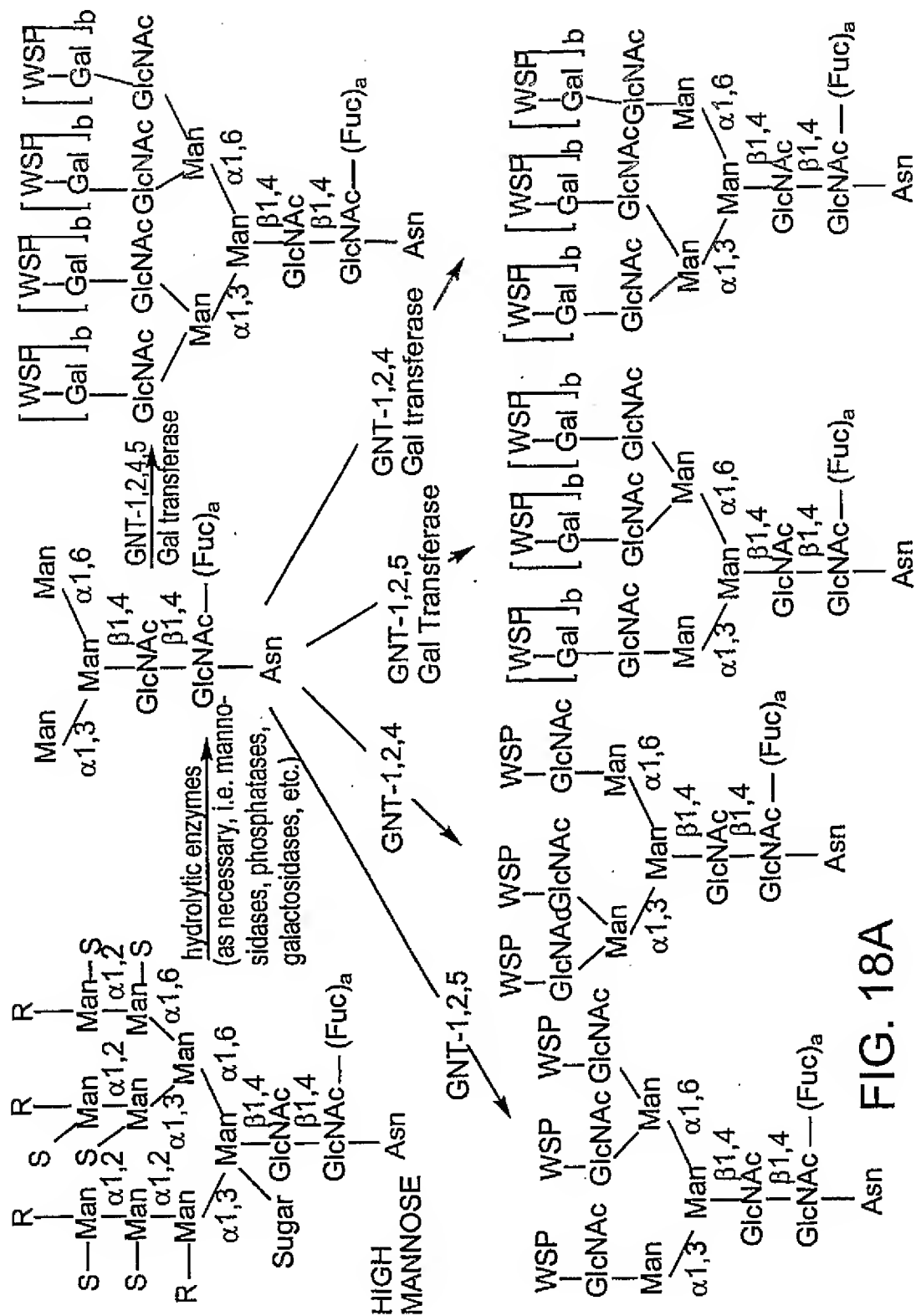


FIG. 17

18/497





19/497

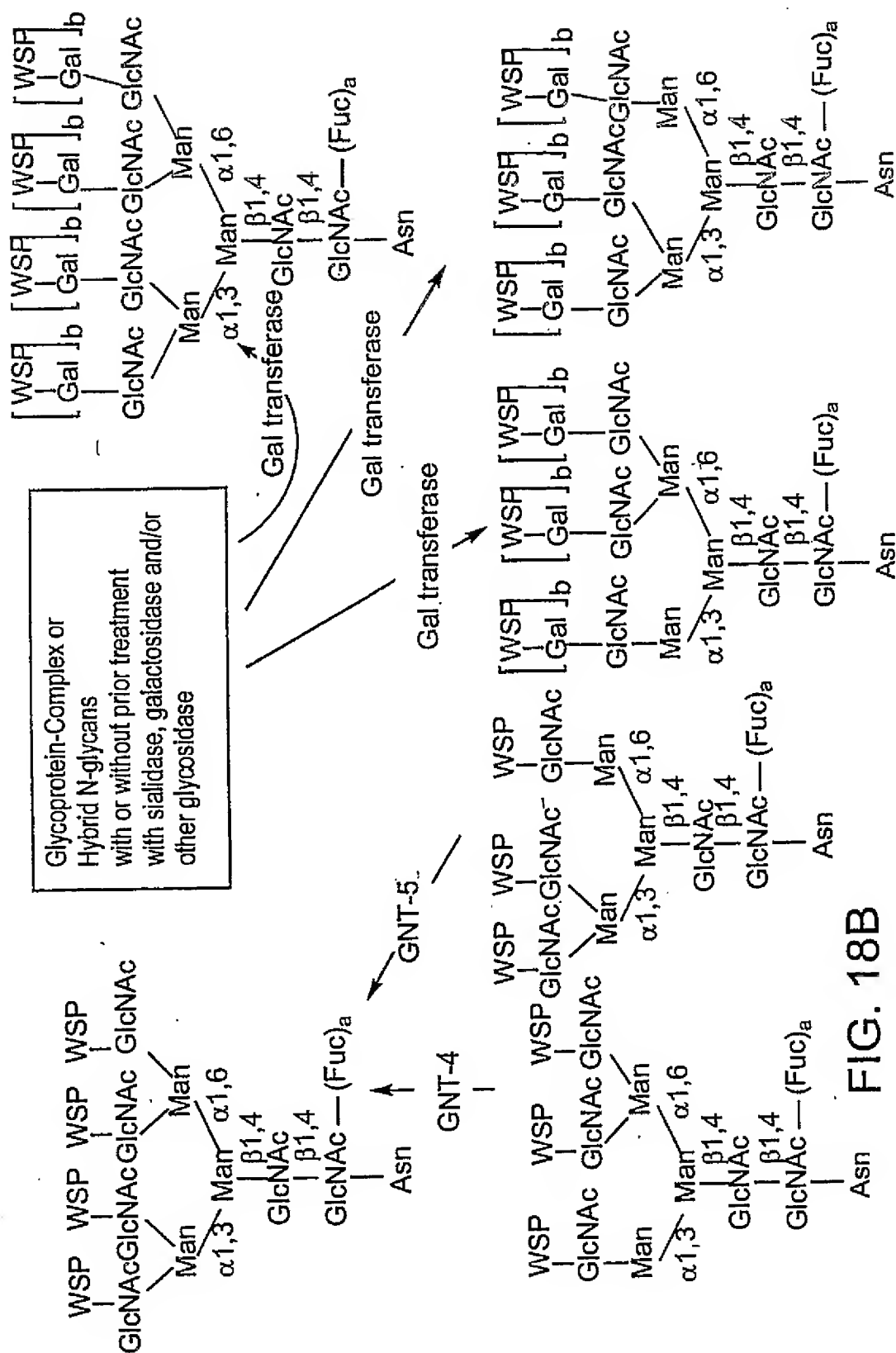
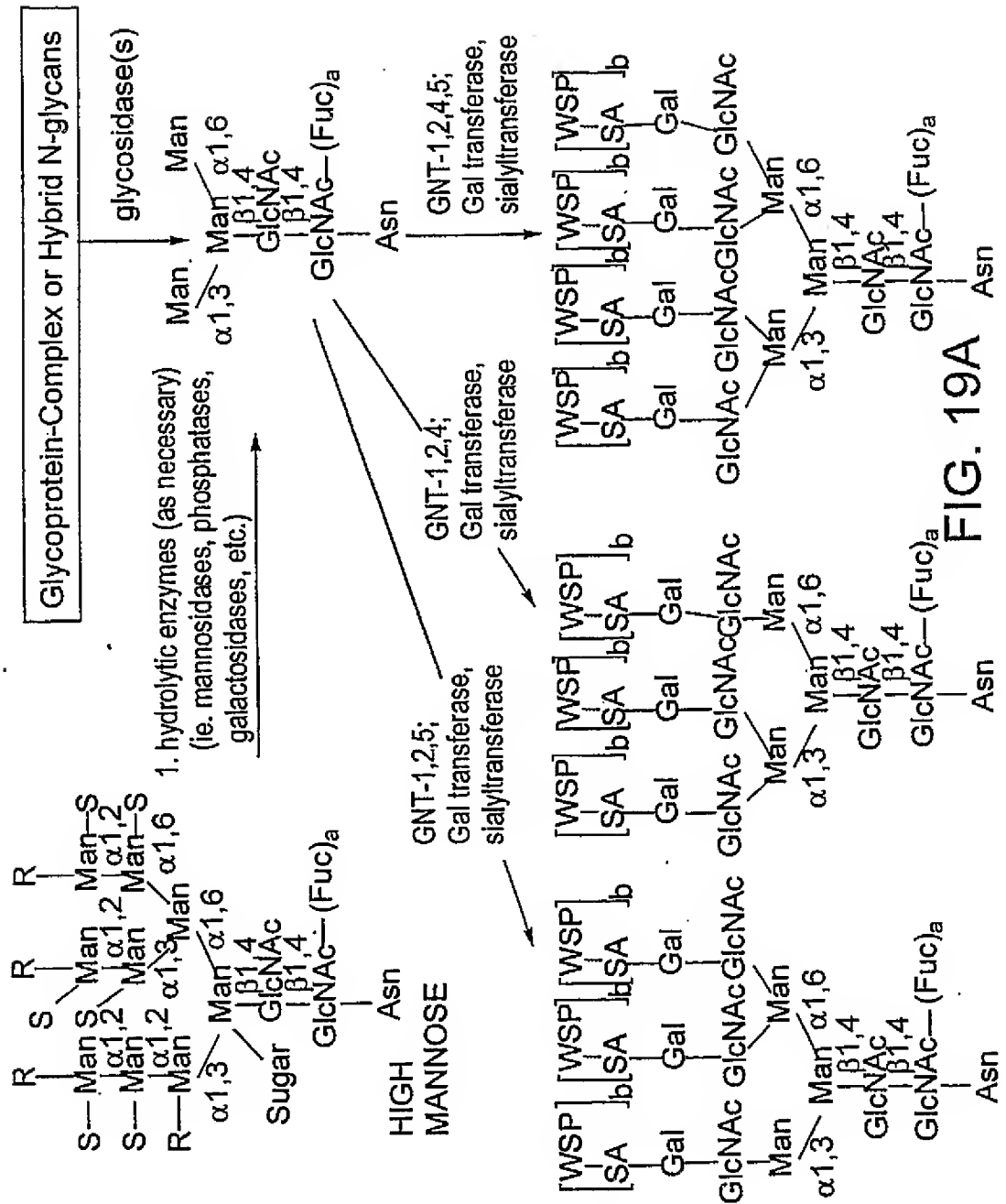
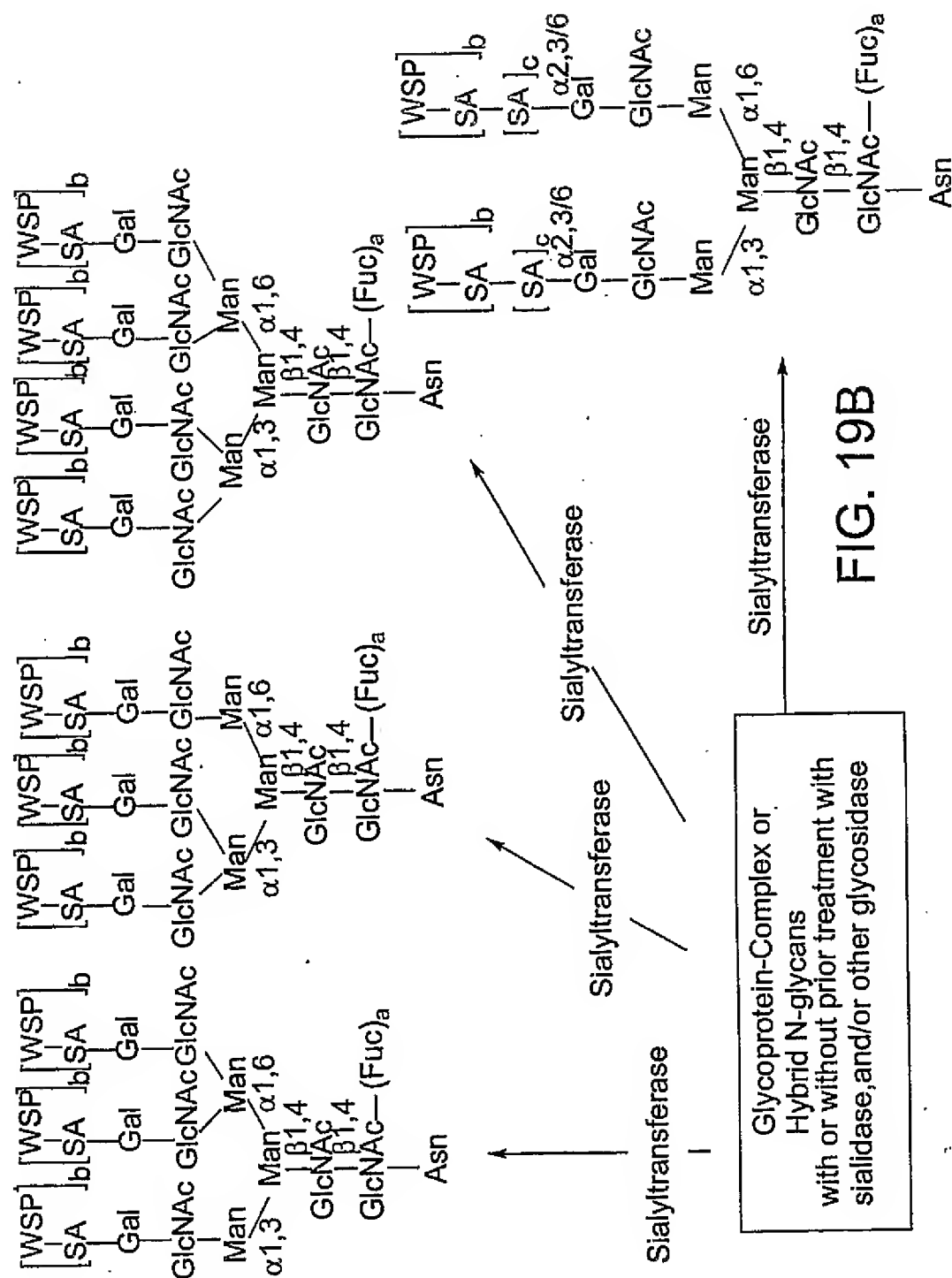


FIG. 18B

20/497



21/497



22/497

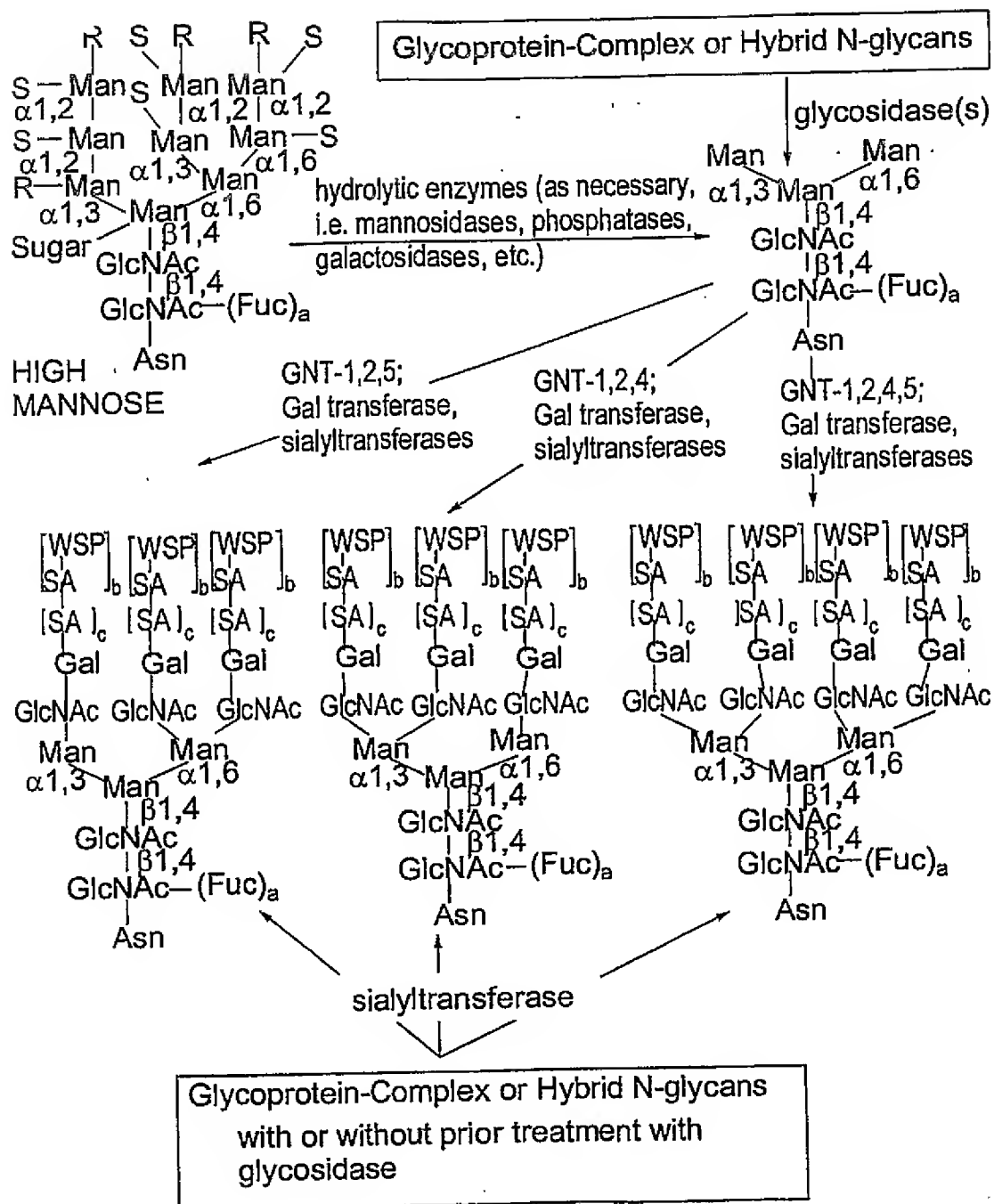
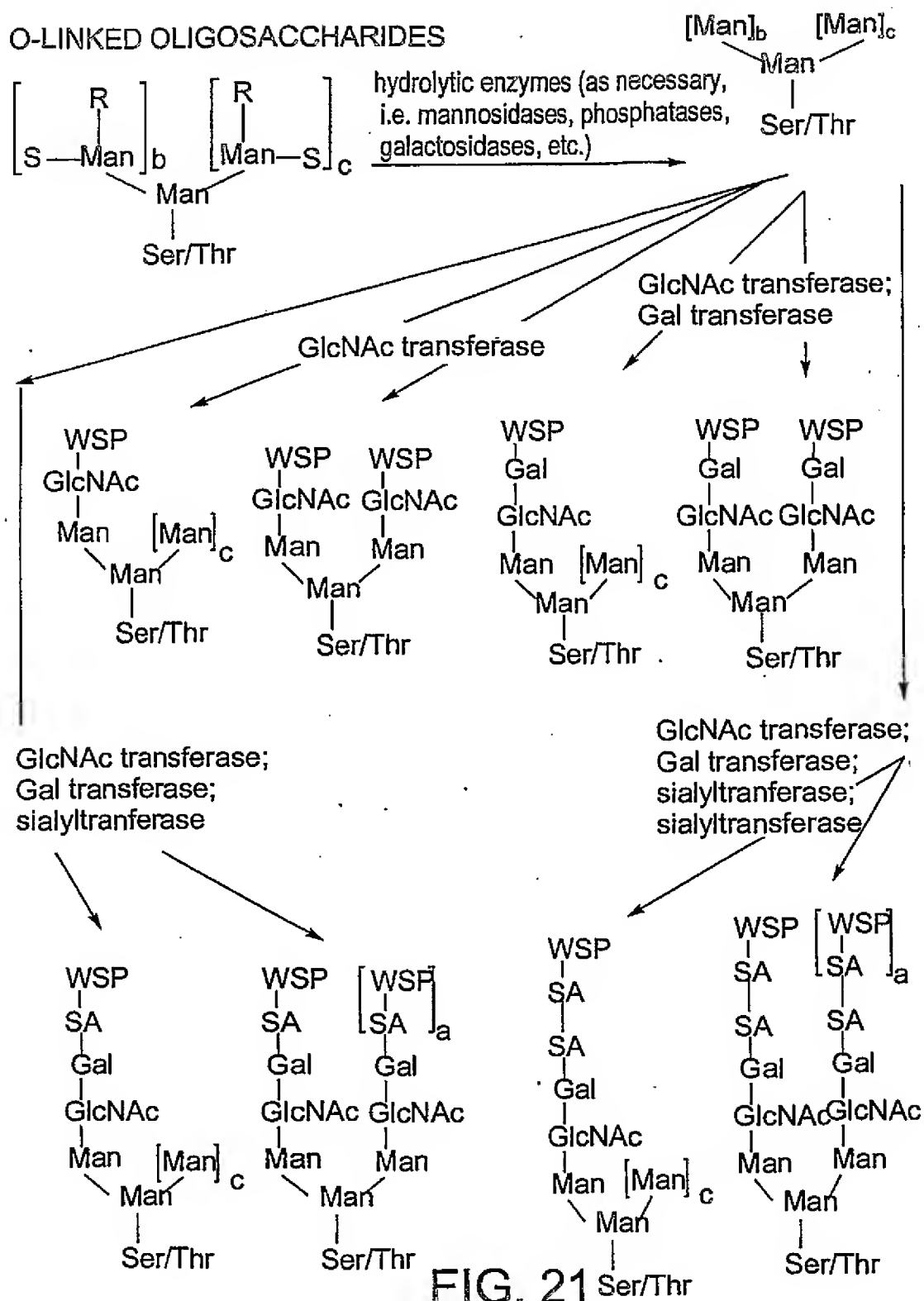


FIG. 20

23/497



**FIG. 21** Ser/Thr

24/497

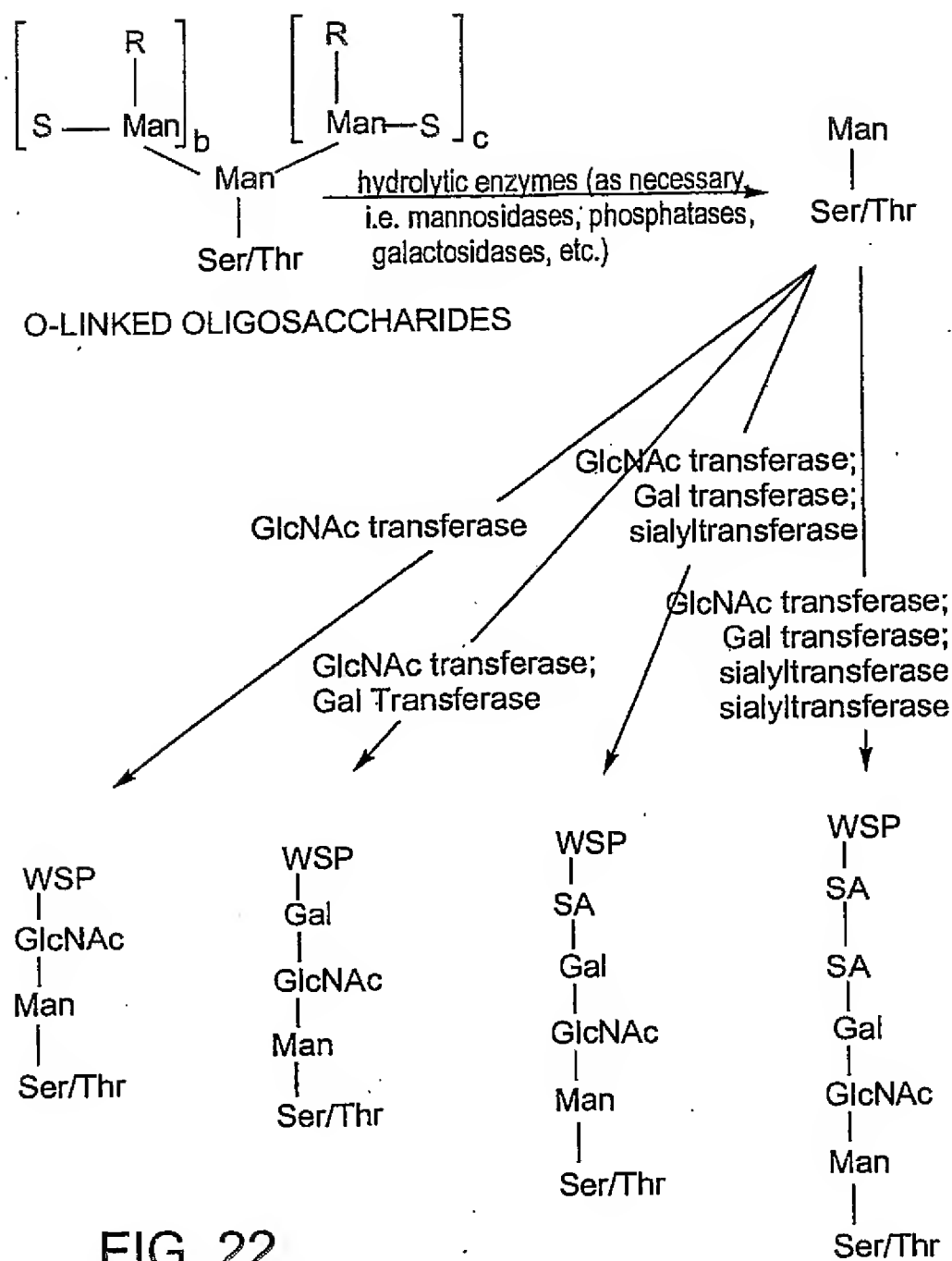


FIG. 22

25/497

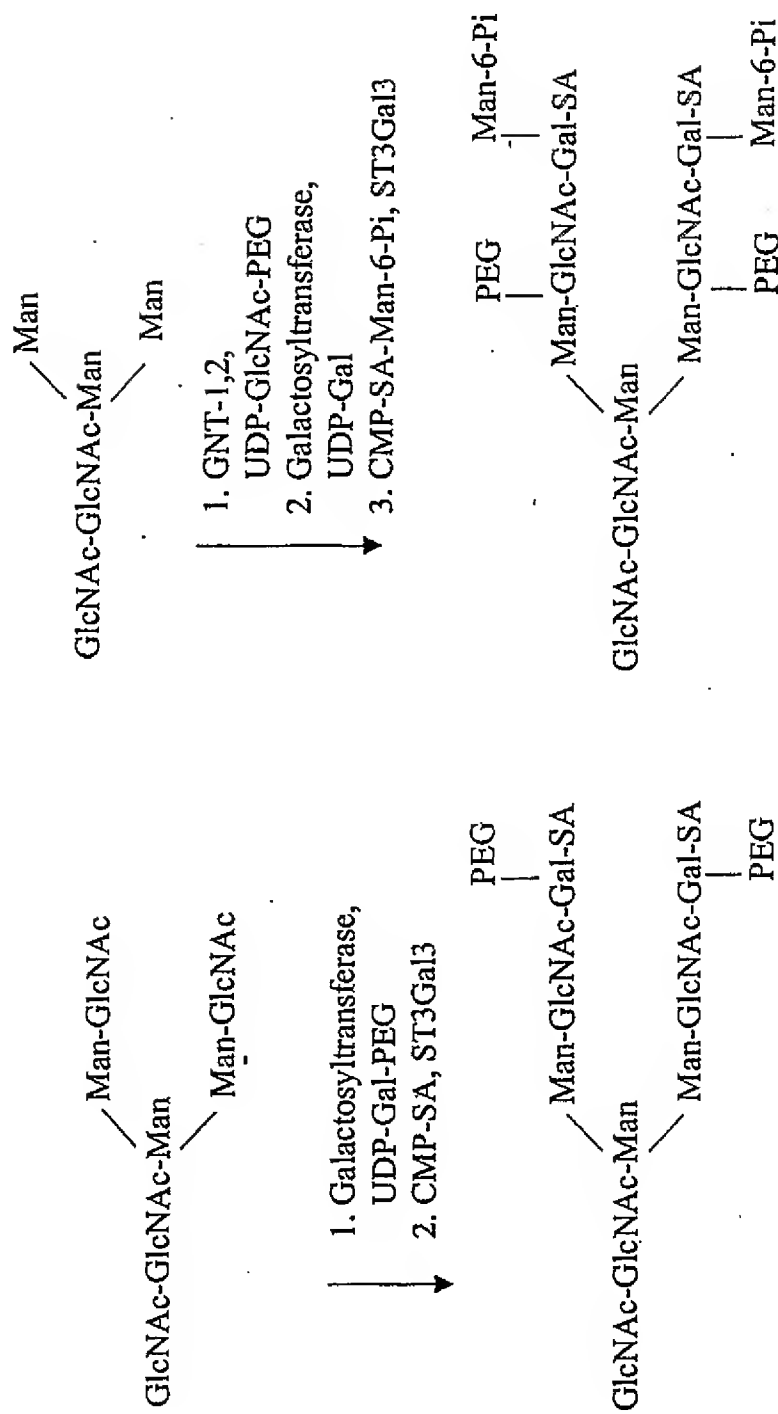


FIG. 23A

FIG. 23B

26/497

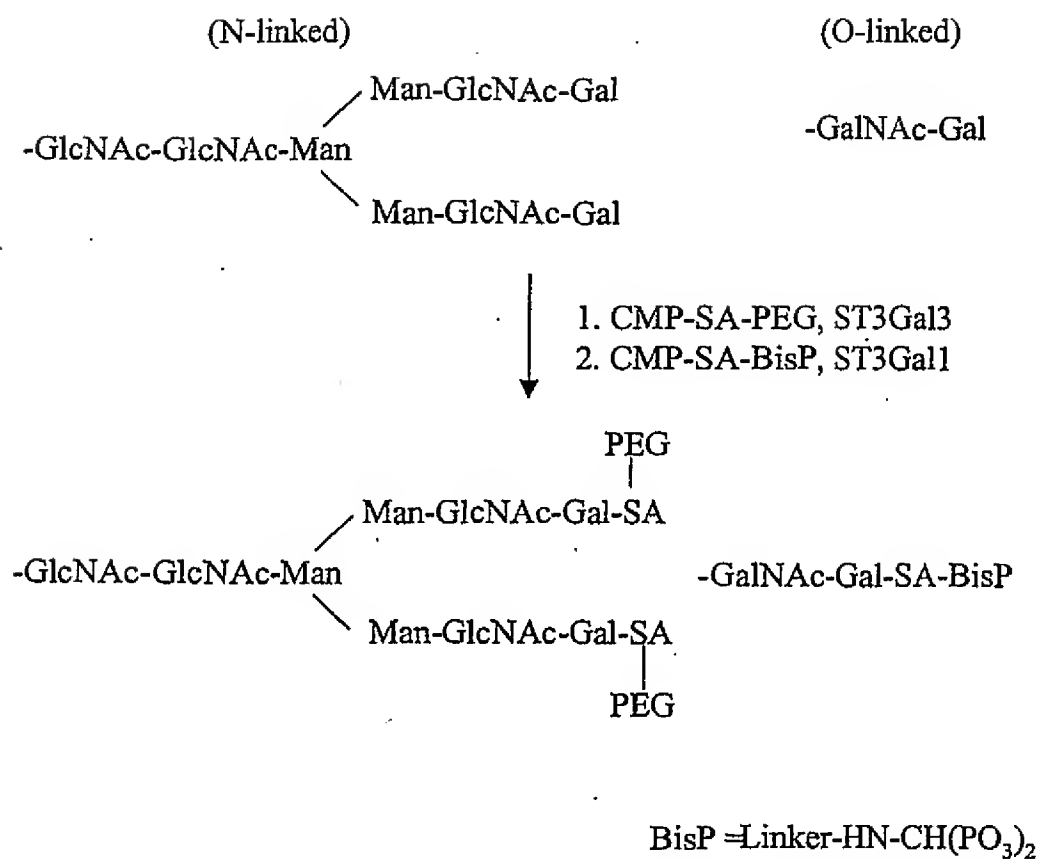


FIG. 23C



27/497

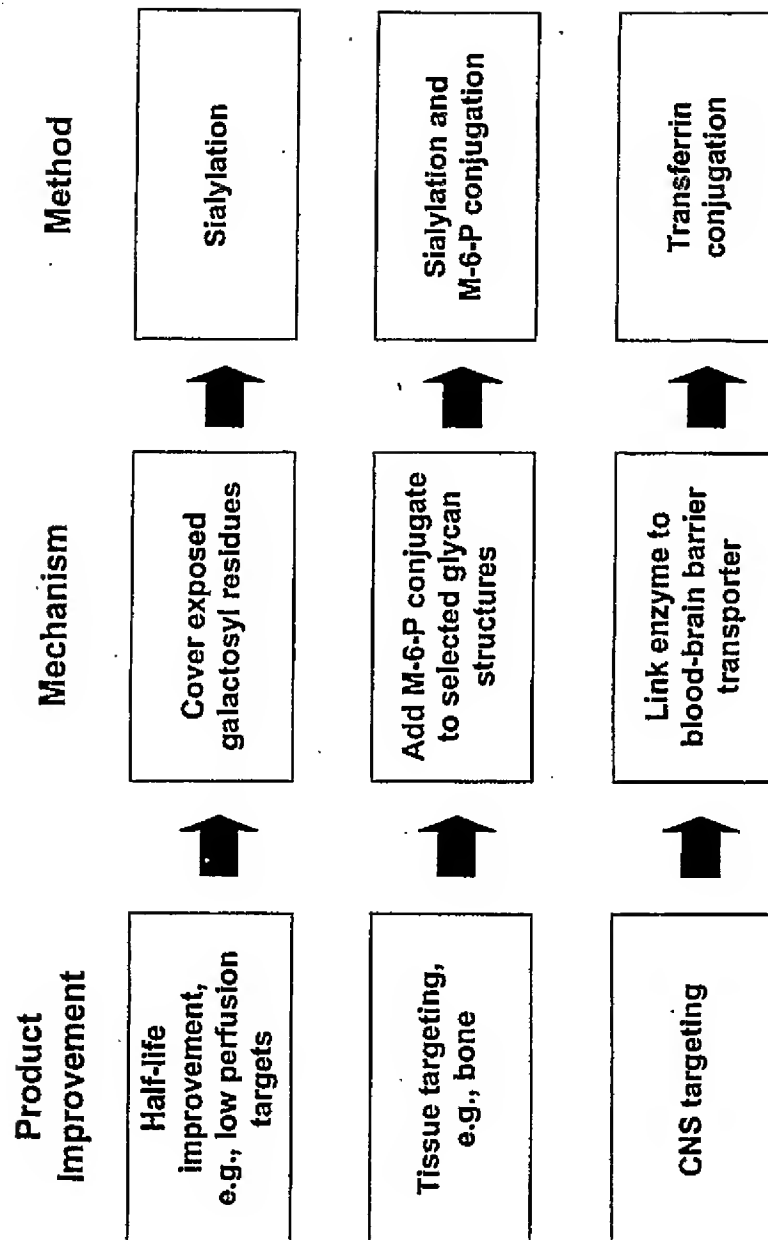


FIG. 24

28/497

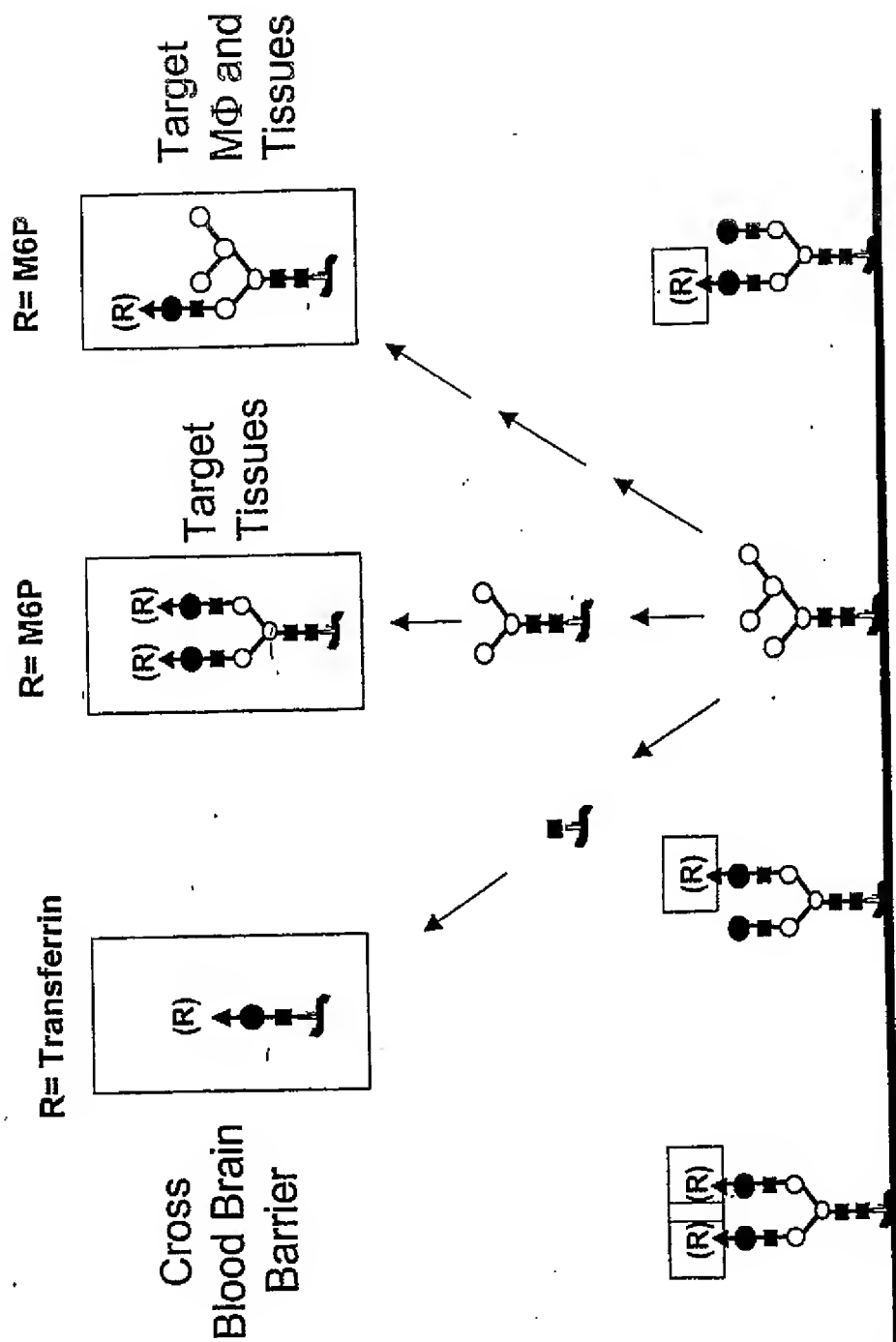


FIG. 25

29/497

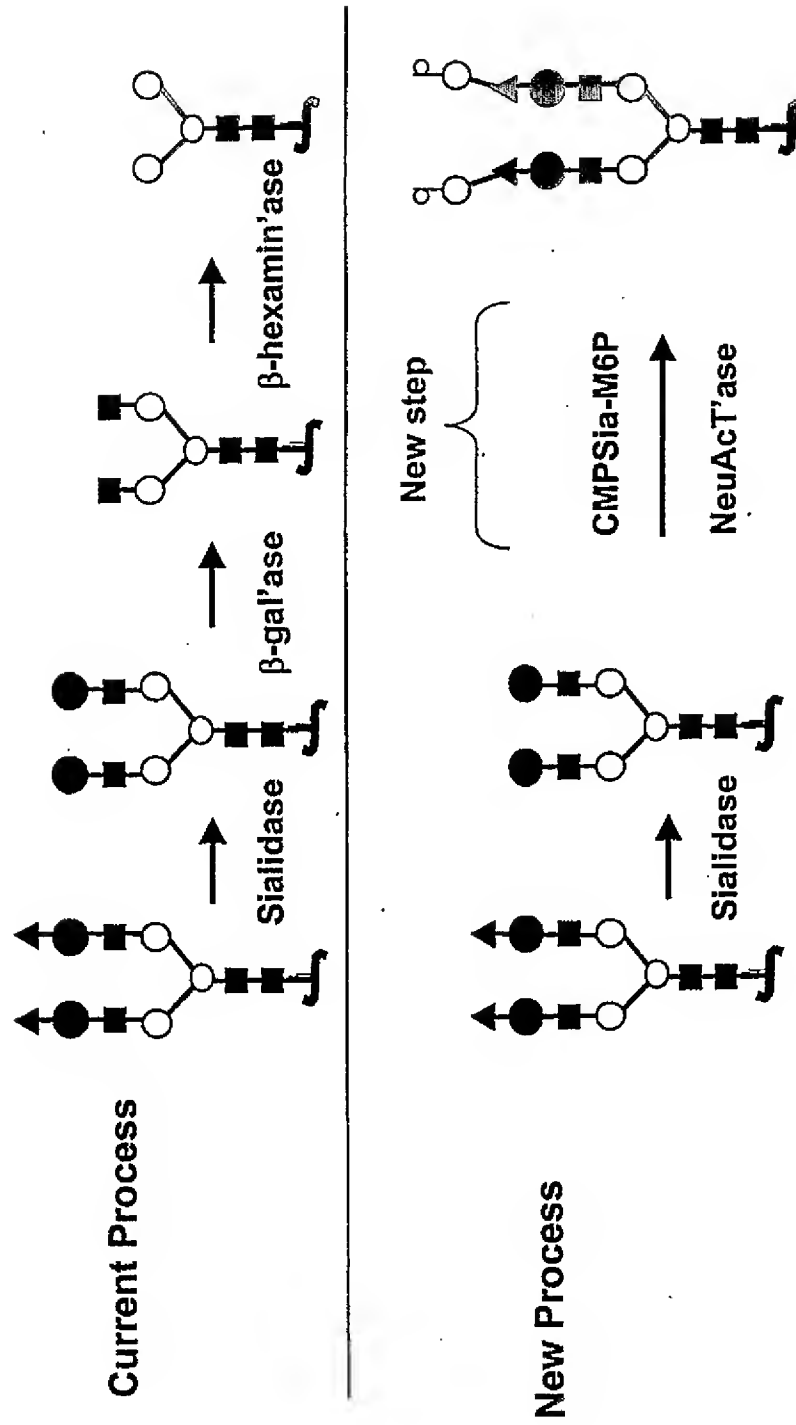


FIG. 26

30/497

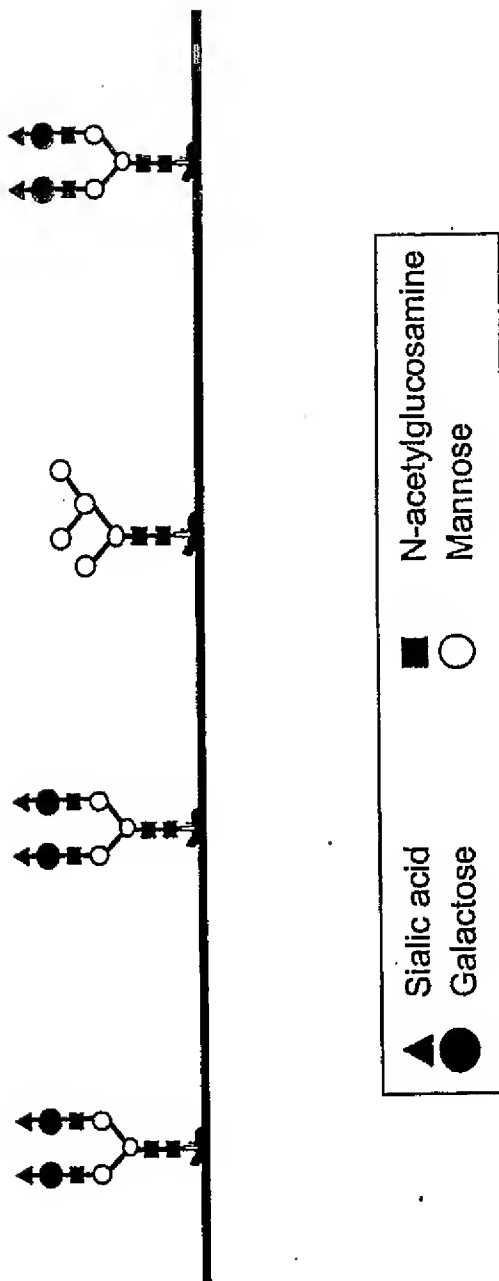


FIG. 27

31/497

|                                            |                                           |
|--------------------------------------------|-------------------------------------------|
| 12AP1/E5 -- Viventia Biotech               | AI-201 -- AutoImmune                      |
| 1964 -- Aventis                            | AI-301 -- AutoImmune                      |
| 20K growth hormone -- AMUR                 | AIDS vaccine -- ANRS, CIBG, Hesed         |
| 28P6/E6 -- Viventia Biotech                | Biomed, Hollis-Eden, Rome, United         |
| 3-Hydroxyphthaloyl-beta-lactoglobulin --   | Biomedical, American Home Products,       |
| 4-IBB ligand gene therapy --               | Maxygen                                   |
| 64-Cu MAb conjugate TETA-1A3 --            | airway receptor ligand -- IC Innovations  |
| Mallinckrodt Institute of Radiology        | AJW 2 -- Ajinomoto                        |
| 64-Cu MAb conjugate TETA-cT84.66           | AK 30 NGF -- Alkermes                     |
| 64-Cu Trastuzumab TETA conjugate --        | Albuferon -- Human Genome Sciences        |
| Genentech                                  | albumin -- Biogen, DSM Anti-Infectives,   |
| A 200 -- Amgen                             | Genzyme Transgenics, PPL Therapeutics,    |
| A10255 -- Eli Lilly                        | TranXenoGen, Welfide Corp.                |
| A1PDX -- Hedral Therapeutics               | aldesleukin -- Chiron                     |
| A6 -- Angstrom                             | alefacept -- Biogen                       |
| aaAT-III -- Genzyme                        | Alentuzumab                               |
| Abciximab -- Centocor                      | Allergy therapy -- ALK-Abello/Maxygen,    |
| ABI.001 -- Atlantic BioPharmaceuticals     | ALK-Abello/RP Scherer                     |
| ABT-828 -- Abbott                          | allergy vaccines -- Allergy Therapeutics  |
| Accutin                                    | Alnidofibatide -- Aventis Pasteur         |
| Actinohivin                                | Alnorine -- SRC VB VECTOR                 |
| activin -- Biotech Australia, Human        | ALP 242 -- Gruenenthal                    |
| Therapeutics, Curis                        | Alpha antitrypsin -- Arriva/Hyland        |
| AD 439 -- Tanox                            | Immuno/ProMetic/Protease Sciences         |
| AD 519 -- Tanox                            | Alpha-1 antitrypsin -- Cutter, Bayer, PPL |
| Adalimumab -- Cambridge Antibody Tech.     | Therapeutics, Profile, ZymoGenetics,      |
| Adenocarcinoma vaccine -- Biomira -- NIS   | Arriva                                    |
| Adenosine deaminase -- Enzond              | Alpha-1 protease inhibitor -- Genzyme     |
| Adenosine A2B receptor antagonists --      | Transgenics, Welfide Corp.                |
| Adenosine Therapeutics                     | Alpha-galactose fusion protein --         |
| ADP-001 -- Axis Genetics                   | Immunomedics                              |
| AF 13948 -- Affymax                        | Alpha-galactosidase A -- Research         |
| Afelimomab -- Knoll                        | Corporation Technologies, Genzyme         |
| AFP-SCAN -- Immunomedics                   | Alpha-glucosidase -- Genzyme, Novazyme    |
| AG 2195 -- Corixa                          | Alpha-lactalbumin                         |
| agalsidase alfa -- Transkaryotic Therapies | Alpha-L-iduronidase -- Transkaryotic      |
| agalsidase beta -- Genzyme                 | Therapies, BioMarin                       |
| AGENT-- Antisoma                           | alteplase -- Genentech                    |
| AI 300 -- AutoImmune                       | alvircept sudotox -- NIH                  |
| AI-101 -- Teva                             | ALX1-11 --sNPS Pharmaceuticals            |
| AI-102 -- Teva                             | Alzheimer's disease gene therapy          |

FIG. 28A

32/497

|                                                    |                                              |
|----------------------------------------------------|----------------------------------------------|
| AM-133 -- AMRAD                                    | Anti-angiogenesis monoclonal antibodies --   |
| Amb a 1 immunostim conj. -- Dynavax                | KS Biomedix/Schering AG                      |
| AMD 3100 -- AnorMED -- NIS                         | Anti-B4 MAb-DC1 conjugate -- ImmunoGen       |
| AMD 3465 -- AnorMED -- NIS                         | Anti-B7 antibody PRIMATIZED -- IDEC          |
| AMD 3465 -- AnorMED -- NIS                         | Anti-B7-1 MAb 16-10A1                        |
| AMD Fab -- Genentech                               | Anti-B7-1 MAb 1G10                           |
| Amediplase -- Menarini, Novartis                   | Anti-B7-2 MAb GL-1                           |
| AM-F9                                              | Anti-B7-2-gelonin immunotoxin --             |
| Amoebiasis vaccine                                 | Antibacterials/antifungals --                |
| Amphiregulin -- Octagene                           | Diversa/IntraBiotics                         |
| anakinra -- Amgen                                  | Anti-beta-amyloid monoclonal antibodies --   |
| analgesic -- Nobex                                 | Cambridge Antibody Tech., Wyeth-Ayerst       |
| ancestim -- Amgen                                  | Anti-BLyS antibodies -- Cambridge            |
| AnergiX.RA -- Corixa, Organon                      | Antibody Tech. /Human Genome Sciences        |
| Angiocidin -- InKine                               | Antibody-drug conjugates -- Seattle          |
| angiogenesis inhibitors -- ILEX                    | Genetics/Eos                                 |
| AngioMab -- Antisoma                               | Anti-C5 MAb BB5-1 -- Alexion                 |
| Angiopoietins -- Regeneron/Procter &               | Anti-C5 MAb N19-8 -- Alexion                 |
| Gamble                                             | Anti-C8 MAb                                  |
| angiostatin -- EntreMed                            | anticancer cytokines -- BioPulse             |
| Angiostatin/endostatin gene therapy --             | anticancer matrix -- Telios Integra          |
| Genetix Pharmaceuticals                            | Anticancer monoclonal antibodies -- ARIUS,   |
| angiotensin-II, topical -- Maret                   | Immunex                                      |
| Anthrax -- EluSys Therapeutics/US Army             | anticancer peptides -- Maxygen, Micrologix   |
| Medical Research Institute                         | Anticancer prodrug Tech. -- Alexion          |
| Anthrax vaccine                                    | Antibody Technologies                        |
| Anti platelet-derived growth factor D human        | anticancer Troy-Bodies -- Affite -- Affitech |
| monoclonal antibodies -- CuraGen                   | anticancer vaccine -- NIH                    |
| Anti-17-1A MAb 3622W94 --                          | anticancers -- Epimmune                      |
| GlaxoSmithKline                                    | Anti-CCR5/CXCR4 sheep MAb -- KS              |
| Anti-2C4 MAb -- Genentech                          | Biomedix Holdings                            |
| anti-4-1BB monoclonal antibodies -- Bristol-       | Anti-CD11a MAb KBA --                        |
| Myers Squibb                                       | Anti-CD11a MAb M17                           |
| Anti-Adhesion Platform Tech. -- Cytovax            | Anti-CD11a MAb TA-3 --                       |
| Anti-adipocyte MAb -- Cambridge Antibody           | Anti-CD11a MAb WT.1 --                       |
| Tech./ObeSys                                       | Anti-CD11b MAb -- Pharmacia                  |
| antiallergics -- Maxygen                           | Anti-CD11b MAb LM2                           |
| antiallergy vaccine -- Acambis                     | Anti-CD154 MAb -- Biogen                     |
| Anti-alpha-4-integrin MAb                          | Anti-CD16-anti-CD30 MAb -- Biotest           |
| Anti-alpha $\nu$ $\beta$ 3 integrin MAb -- Applied | Anti-CD18 MAb -- Pharmacia                   |
| Molecular Evolution                                | Anti-CD19 MAb B43 --                         |

FIG. 28B

33/497

|                                                              |                                                                     |
|--------------------------------------------------------------|---------------------------------------------------------------------|
| Anti-CD19 MAb -liposomal sodium butyrate conjugate –         | Anti-CD4 MAb 4162W94 – GlaxoSmithKline                              |
| Anti-CD147                                                   | Anti-CD4 MAb B-F5 – Diaclone                                        |
| Anti-CD19 MAb-saporin conjugate –                            | Anti-CD4 MAb GK1-5                                                  |
| Anti-CD19-dsFv-PE38-immunotoxin –                            | Anti-CD4 MAb KT6                                                    |
| Anti-CD2 MAb 12-15 –                                         | Anti-CD4 MAb OX38                                                   |
| Anti-CD2 MAb B-E2 – Diaclone                                 | Anti-CD4 MAb PAP conjugate – Bristol-Myers Squibb                   |
| Anti-CD2 MAb OX34 –                                          | Anti-CD4 MAb RIB 5-2                                                |
| Anti-CD2 MAb OX54 –                                          | Anti-CD4 MAb W3/25                                                  |
| Anti-CD2 MAb OX55 –                                          | Anti-CD4 MAb YTA 3.1.2                                              |
| Anti-CD2 MAb RM2-1                                           | Anti-CD4 MAb YTS 177-9                                              |
| Anti-CD2 MAb RM2-2                                           | Anti-CD40 ligand MAb 5c8 – Biogen                                   |
| Anti-CD2 MAb RM2-4                                           | Anti-CD40 MAb                                                       |
| Anti-CD20 MAb BCA B20                                        | Anti-CD40 MAb 5D12 – Tanox                                          |
| Anti-CD20-anti-Fc alpha RI bispecific MAb – Medarex, Tenovus | Anti-CD44 MAb A3D8                                                  |
| Anti-CD22 MAb-saporin-6 complex –                            | Anti-CD44 MAb GKWA3                                                 |
| Anti-CD3 immunotoxin –                                       | Anti-CD44 MAb IM7                                                   |
| Anti-CD3 MAb 145-2C11 – Pharming                             | Anti-CD44 MAb KM81                                                  |
| Anti-CD3 MAb CD4IgG conjugate -- Genentech                   | Anti-CD44 variant monoclonal antibodies -- Corixa/Hebrew University |
| Anti-CD3 MAb humanised – Protein Design, RW Johnson          | Anti-CD45 MAb BC8-I-131                                             |
| Anti-CD3 MAb WT32                                            | Anti-CD45RB MAb                                                     |
| Anti-CD3 MAb-ricin-chain-A conjugate –                       | Anti-CD48 MAb HuLy-m3                                               |
| Anti-CD3 MAb-xanthine-oxidase conjugate –                    | Anti-CD48 MAb WM-63                                                 |
| Anti-CD30 MAb BerH2 -- Medac                                 | Anti-CD5 MAb – Becton Dickinson                                     |
| Anti-CD30 MAb-saporin conjugate                              | Anti-CD5 MAb OX19                                                   |
| Anti-CD30-scFv-ETA'-immunotoxin                              | Anti-CD6 MAb                                                        |
| Anti-CD38 MAb AT13/5                                         | Anti-CD7 MAb-PAP conjugate                                          |
| Anti-CD38 MAb-saporin conjugate                              | Anti-CD7 MAb-ricin-chain-A conjugate                                |
| Anti-CD3-anti-CD19 bispecific MAb                            | Anti-CD8 MAb – Amerimmune, Cytodyn, Becton Dickinson                |
| Anti-CD3-anti-EGFR MAb                                       | Anti-CD8 MAb 2-43                                                   |
| Anti-CD3-anti-interleukin-2-receptor MAb                     | Anti-CD8 MAb OX8                                                    |
| Anti-CD3-anti-MOV18 MAb – Centocor                           | Anti-CD80 MAb P16C10 – IDEC                                         |
| Anti-CD3-anti-SCLC bispecific MAb                            | Anti-CD80 MAb P7C10 – ID Vaccine                                    |
| Anti-CD4 idiotype vaccine                                    | Anti-CD8-idarubicin conjugate                                       |
| Anti-CD4 MAb – Centocor, IDEC Pharmaceuticals, Xenova Group  | Anti-CEA MAb CE-25                                                  |
| Anti-CD4 MAb 16H5                                            | Anti-CEA MAb MN 14 – Immunomedics                                   |
|                                                              | Anti-CEA MAb MN14-PE40 conjugate – Immunomedics                     |

FIG. 28C

34/497

|                                                                                |                                                                                       |
|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Anti-CEA MAb T84.66-interleukin-2 conjugate                                    | Anti-heparanase human monoclonal antibodies -- Oxford                                 |
| Anti-CEA sheep MAb -- KS Biomedix Holdings                                     | Glycosciences/Medarex                                                                 |
| Anti-cell surface monoclonal antibodies -- Cambridge Antibody Tech. /Pharmacia | Anti-hepatitis C virus human monoclonal antibodies -- XTL Biopharmaceuticals          |
| Anti-c-erbB2-anti-CD3 bifunctional MAb -- Otsuka                               | Anti-HER-2 antibody gene therapy                                                      |
| Anti-CMV MAb -- Scotgen                                                        | Anti-herpes antibody -- Epicyte                                                       |
| Anti-complement                                                                | Anti-HIV antibody -- Epicyte                                                          |
| Anti-CTLA-4 MAb                                                                | anti-HIV catalytic antibody -- Hesed Biomed                                           |
| Anti-EGFR catalytic antibody -- Hesed Biomed                                   | anti-HIV fusion protein -- Idun                                                       |
| anti-EGFR immunotoxin -- IVAX                                                  | anti-HIV proteins -- Cangene                                                          |
| Anti-EGFR MAb -- Abgenix                                                       | Anti-HM1-24 MAb -- Chugai                                                             |
| Anti-EGFR MAb 528                                                              | Anti-hR3 MAb                                                                          |
| Anti-EGFR MAb KSB 107 -- KS Biomedix                                           | Anti-Human-Carcinoma-Antigen MAb -- Epicyte                                           |
| Anti-EGFR MAb-DM1 conjugate -- ImmunoGen                                       | Anti-ICAM-1 MAb -- Boehringer Ingelheim                                               |
| Anti-EGFR MAb-LA1 --                                                           | Anti-ICAM-1 MAb 1A-29 -- Pharmacia                                                    |
| Anti-EGFR sheep MAb -- KS Biomedix                                             | Anti-ICAM-1 MAb HA58                                                                  |
| Anti-FAP MAb F19-I-131                                                         | Anti-ICAM-1 MAb YN1/1.7.4                                                             |
| Anti-Fas IgM MAb CH11                                                          | Anti-ICAM-3 MAb ICM3 -- ICOS                                                          |
| Anti-Fas MAb Jo2                                                               | Anti-idiotypic breast cancer vaccine 11D10                                            |
| Anti-Fas MAb RK-8                                                              | Anti-idiotypic breast cancer vaccine ACA14C5 --                                       |
| Anti-Fit-1 monoclonal antibodies -- ImClone                                    | Anti-idiotypic cancer vaccine -- ImClone Systems/Merck KGaA ImClone, Viventia Biotech |
| Anti-fungal peptides -- State University of New York                           | Anti-idiotypic cancer vaccine 1A7 -- Titan                                            |
| antifungal tripeptides -- BTG                                                  | Anti-idiotypic cancer vaccine 3H1 -- Titan                                            |
| Anti-ganglioside GD2 antibody-interleukin-2 fusion protein -- Lexigen          | Anti-idiotypic cancer vaccine TriAb -- Titan                                          |
| Anti-GM2 MAb -- Kyowa                                                          | Anti-idiotypic Chlamydia trachomatis vaccine                                          |
| Anti-GM-CSF receptor monoclonal antibodies -- AMRAD                            | Anti-idiotypic colorectal cancer vaccine -- Novartis                                  |
| Anti-gp130 MAb -- Tosoh                                                        | Anti-idiotypic colorectal cancer vaccine -- Onyvax                                    |
| Anti-HCA monoclonal antibodies -- AltaRex/Epigen                               | Anti-idiotypic melanoma vaccine -- IDEC Pharmaceuticals                               |
| Anti-hCG antibodies -- Abgenix/AVI BioPharma                                   | Anti-idiotypic ovarian cancer vaccine ACA 125                                         |
|                                                                                | Anti-idiotypic ovarian cancer vaccine AR54 - AltaRex                                  |

FIG. 28D



35/497

|                                                                       |                                                                                            |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Anti-idiotypic ovarian cancer vaccine CA-125 -- AltaRex, Biomira      | Anti-L-selectin monoclonal antibodies -- Protein Design Labs, Abgenix, Stanford University |
| Anti-IgE catalytic antibody -- Hersed Biomed                          | Anti-MBL monoclonal antibodies -- Alexion/Brigham and Women's Hospital                     |
| Anti-IgE MAb E26 -- Genentech                                         | Anti-MHC monoclonal antibodies                                                             |
| Anti-IGF-1 MAb                                                        | Anti-MIF antibody humanised -- IDEC, Cytokine PharmaSciences                               |
| anti-inflammatory -- GeneMax                                          | Anti-MRSA/VRSA sheep MAb -- KS Biomedix Holdings                                           |
| anti-inflammatory peptide -- BTG                                      | Anti-mu MAb -- Novartis                                                                    |
| anti-integrin peptides -- Burnha                                      | Anti-MUC-1 MAb                                                                             |
| Anti-interferon-alpha-receptor MAb 64G12 -- Pharma Pacific Management | Anti-MUC 18                                                                                |
| Anti-interferon-gamma MAb -- Protein Design Labs                      | Anti-Nogo-A MAb IN1                                                                        |
| Anti-interferon-gamma polyclonal antibody - Advanced Biotherapy       | Anti-nuclear autoantibodies -- Procyon                                                     |
| Anti-interleukin-10 MAb --                                            | Anti-ovarian cancer monoclonal antibodies - Dompe                                          |
| Anti-interleukin-12 MAb --                                            | Anti-p185 monoclonal antibodies                                                            |
| Anti-interleukin-1-beta polyclonal antibody -- R&D Systems            | Anti-p43 MAb                                                                               |
| Anti-interleukin-2 receptor MAb 2A3                                   | Antiparasitic vaccines                                                                     |
| Anti-interleukin-2 receptor MAb 33B3-1 -- Immunotech                  | Anti-PDGF/bFGF sheep MAb -- KS Biomedix                                                    |
| Anti-interleukin-2 receptor MAb ART-18                                | Anti-properdin monoclonal antibodies -- Abgenix/Gliatech                                   |
| Anti-interleukin-2 receptor MAb LO-Tact-1                             | Anti-PSMA (prostate specific membrane antigen)                                             |
| Anti-interleukin-2 receptor MAb Mikbeta1                              | Anti-PSMA MAb J591 -- BZL Biologics                                                        |
| Anti-interleukin-2 receptor MAb NDS61                                 | Anti-Rev MAb gene therapy --                                                               |
| Anti-interleukin-4 MAb 11B11                                          | Anti-RSV antibodies -- Epicyte, Intracell                                                  |
| Anti-interleukin-5 MAb -- Wallace Laboratories                        | Anti-RSV monoclonal antibodies -- Medarex/MedImmune, Applied Molecular Evolution/MedImmune |
| Anti-interleukin-6 MAb -- Centocor, Diaclone, Pharmadigm              | Anti-RSV MAb, inhalation -- Alkermes/MedImmune                                             |
| Anti-interleukin-8 MAb -- Abgenix                                     | Anti-RT gene therapy                                                                       |
| Anti-interleukin-8 MAb -- Xenotech                                    | Antisense K-ras RNA gene therapy                                                           |
| Anti-JL1 MAb                                                          | Anti-SF-25 MAb                                                                             |
| Anti-Klebsiella sheep MAb -- KS Biomedix Holdings                     | Anti-sperm antibody -- Epicyte                                                             |
| Anti-Laminin receptor MAb-liposomal doxorubicin conjugate             | Anti-Tac(Fv)-PE38 conjugate                                                                |
| Anti-LCG MAb -- Cytoclonal                                            | Anti-TAPA/CD81 MAb AMP1                                                                    |
| Anti-lipopolysaccharide MAb -- VitaResc                               | Anti-tat gene therapy                                                                      |

FIG. 28E

36/497

|                                                                                   |                                                                              |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Anti-TCR-alphabeta MAb H57-597                                                    | AOP-RANTES – Senetek                                                         |
| Anti-TCR-alphabeta MAb R73                                                        | Apan-CH – Praecis Pharmaceuticals                                            |
| Anti-tenascin MAb BC-4-I-131                                                      | APC-8024 – Demegen                                                           |
| Anti-TGF-beta human monoclonal antibodies – Cambridge Antibody Tech., Genzyme     | ApoA-1 – Milano, Pharmacia                                                   |
| Anti-TGF-beta MAb 2G7 – Genentech                                                 | Apogen – Alexion                                                             |
| Antithrombin III – Genzyme Transgenics, Aventis, Bayer, Behringwerke, CSL, Myriad | apolipoprotein A1 – Avanir                                                   |
| Anti-Thy1 MAb                                                                     | Apolipoprotein E – Bio-Tech. General                                         |
| Anti-Thy1.1 MAb                                                                   | Applaggin – Biogen                                                           |
| Anti-tissue factor/factor VIIA sheep MAb – KS Biomedix                            | aprotinin – ProdiGene                                                        |
| Anti-TNF monoclonal antibodies – Centocor, Chiron, Peptech, Pharacia, Serono      | APT-070C – AdProTech                                                         |
| Anti-TNF sheep MAb – KS Biomedix Holdings                                         | AR 177 – Aronex Pharmaceuticals                                              |
| Anti-TNFalpha MAb – Genzyme                                                       | AR 209 – Aronex Pharmaceuticals, Antigenics                                  |
| Anti-TNFalpha MAb B-C7 – Diaclone                                                 | AR545C                                                                       |
| Anti-tooth decay MAb – Planet BioTech.                                            | ARGENT gene delivery systems – ARIAD                                         |
| Anti-TRAIL receptor-1 MAb – Takeda                                                | Arresten                                                                     |
| Antitumour RNases – NIH                                                           | ART-123 – Asahi Kasei                                                        |
| Anti-VCAM MAb 2A2 – Alexion                                                       | arylsulfatase B – BioMarin                                                   |
| Anti-VCAM MAb 3F4 – Alexion                                                       | Arylsulfatase B, Recombinant human – BioMarin                                |
| Anti-VCAM-1 MAb                                                                   | AS 1051 – Ajinomoto                                                          |
| Anti-VEC MAb – ImClone                                                            | ASI-BCL – Intracell                                                          |
| Anti-VEGF MAb – Genentech                                                         | Asparaginase – Merck                                                         |
| Anti-VEGF MAb 2C3                                                                 | ATL-101 – Alizyme                                                            |
| Anti-VEGF sheep MAb – KS Biomedix Holdings                                        | Atrial natriuretic peptide – Pharis                                          |
| Anti-VLA-4 MAb HP1/2 – Biogen                                                     | Aurintricarboxylic acid-high molecular weight                                |
| Anti-VLA-4 MAb PS/2                                                               | Autoimmune disorders – GPC                                                   |
| Anti-VLA-4 MAb R1-2                                                               | Biotech/MorphoSys                                                            |
| Anti-VLA-4 MAb TA-2                                                               | Autoimmune disorders and transplant rejection – Bristol-Myers Squibb/Genzyme |
| Anti-VAP-1 human MAb                                                              | Tra                                                                          |
| Anti-VRE sheep MAb – KS Biomedix Holdings                                         | Autoimmune disorders/cancer – Abgenix/Chiron, CuraGen                        |
| ANUP – TranXenoGen                                                                | Autotaxin                                                                    |
| ANUP-1 – Pharis                                                                   | Avicidin – NeoRx                                                             |
|                                                                                   | axogenesis factor-1 – Boston Life Sciences                                   |
|                                                                                   | Axokine – Regeneron                                                          |
|                                                                                   | B cell lymphoma vaccine – Biomira                                            |
|                                                                                   | B7-1 gene therapy –                                                          |
|                                                                                   | BABS proteins – Chiron                                                       |

FIG. 28F

37/497

|                                              |                                             |
|----------------------------------------------|---------------------------------------------|
| BAM-002 -- Novelos Therapeutics              | BMP 2 -- Genetics Institute/Medtronic-      |
| Basiliximab (anti CD25 MAb) -- Novartis      | Sofamor Danek, Genetics Institute/          |
| Bay-16-9996 -- Bayer                         | Collagenesis, Genetics                      |
| Bay-39-9437 -- Bayer                         | Institute/Yamanouch                         |
| Bay-50-4798 -- Bayer                         | BMP 2 gene therapy                          |
| BB-10153 -- British Biotech                  | BMP 52 -- Aventis Pasteur, Biopharm         |
| BBT-001 -- Bolder BioTech.                   | BMP-2 -- Genetics Institute                 |
| BBT-002 -- Bolder BioTech.                   | BMS 182248 -- Bristol-Myers Squibb          |
| BBT-003 -- Bolder BioTech.                   | BMS 202448 -- Bristol-Myers Squibb          |
| BBT-004 -- Bolder BioTech.                   | bone growth factors -- IsoTis               |
| BBT-005 -- Bolder BioTech.                   | BPC-15 -- Pfizer                            |
| BBT-006 -- Bolder BioTech.                   | brain natriuretic peptide --                |
| BBT-007 -- Bolder BioTech.                   | Breast cancer -- Oxford                     |
| BCH-2763 -- Shire                            | GlycoSciences/Medarex                       |
| BCSF -- Millenium Biologix                   | Breast cancer vaccine -- Therion Biologics, |
| BDNF -- Regeneron -- Amgen                   | Oregon                                      |
| Becaplermin -- Johnson & Johnson, Chiron     | BSSL -- PPL Therapeutics                    |
| Bectumomab -- Immunomedics                   | BST-2001 -- BioStratum                      |
| Beriplast -- Aventis                         | BST-3002 -- BioStratum                      |
| Beta-adrenergic receptor gene therapy --     | BTI 322 --                                  |
| University of Arkansas                       | butyrylcholinesterase -- Shire              |
| bFGF -- Scios                                | C 6822 -- COR Therapeutics                  |
| BI 51013 -- Behringwerke AG                  | C1 esterase inhibitor -- Pharming           |
| BIBH 1 -- Boehringer Ingelheim               | C3d adjuvant -- AdProTech                   |
| BIM-23190 -- Beaufour-Ipsen                  | CAB-2.1 -- Millennium                       |
| birch pollen immunotherapy -- Pharmacia      | calcitonin -- Inhale Therapeutics Systems,  |
| bispecific fusion proteins -- NIH            | Aventis, Genetronics, TranXenoGen,          |
| Bispecific MAb 2B1 -- Chiron                 | Unigene, Rhone Poulenc Rohrer               |
| Bitistatin                                   | calcitonin -- oral -- Nobex, Emisphere,     |
| BIWA 4 -- Boehringer Ingelheim               | Pharmaceutical Discovery                    |
| blood substitute -- Northfield, Baxter Intl. | Calcitonin gene-related peptide -- Asahi    |
| BLP-25 -- Biomira                            | Kasei -- Unigene                            |
| BLS-0597 -- Boston Life Sciences             | calcitonin, human -- Suntory                |
| BLyS -- Human Genome Sciences                | calcitonin, nasal -- Novartis, Unigene      |
| BLyS radiolabelled -- Human Genome           | calcitonin, Panoderm -- Elan                |
| Sciences                                     | calcitonin, Peptitrol -- Shire              |
| BM 06021 -- Boehringer Mannheim              | calcitonin, salmon -- Therapicon            |
| BM-202 -- BioMarin                           | calin -- Biopharm                           |
| BM-301 -- BioMarin                           | Calphobindin I                              |
| BM-301 -- BioMarin                           | calphobindin I -- Kowa                      |
| BM-302 -- BioMarin                           | calreticulin -- NYU                         |

FIG. 28G

38/497

|                                            |                                         |
|--------------------------------------------|-----------------------------------------|
| Campath-1G                                 | CD4 fusion toxin -- Senetek             |
| Campath-1M                                 | CD4 IgG -- Genentech                    |
| cancer therapy -- Cangene                  | CD4 receptor antagonists --             |
| cancer vaccine -- Aixlie, Aventis Pasteur, | Pharmacoepia/Progenics                  |
| Center of Molecular Immunology, YM         | CD4 soluble -- Progenics                |
| BioSciences, Cytos, Genzyme,               | CD4, soluble -- Genzyme Transgenics     |
| Transgenics, GlobelImmune, Igeneon,        | CD40 ligand -- Immunex                  |
| ImClone, Virogenetics, InterCell, Iomai,   | CD4-ricin chain A -- Genentech          |
| Jenner Biotherapies, Memorial Sloan-       | CD59 gene therapy -- Alexion            |
| Kettering Cancer Center, Sydney Kimmel     | CD8 TIL cell therapy -- Aventis Pasteur |
| Cancer Center, Novavax, Protein            | CD8, soluble -- Avidex                  |
| Sciences, Argonex, SIGA                    | CD95 ligand -- Roche                    |
| Cancer vaccine ALVAC-CEA B7.1 --           | CDP 571 -- Celltech                     |
| Aventis Pasteur/Therion Biologics          | CDP 850 -- Celltech                     |
| Cancer vaccine CEA-TRICOM -- Aventis       | CDP-860 (PEG-PDGF MAb) -- Celltech      |
| Pasteur/Therion Biologics                  | CDP 870 -- Celltech                     |
| Cancer vaccine gene therapy -- Cantab      | CDS-1 -- Ernest Orlando                 |
| Pharmaceuticals                            | Cedelizumab -- Ortho-McNeil             |
| Cancer vaccine HER-2/neu -- Corixa         | Cetermin -- Insmed                      |
| Cancer vaccine THERATOPE -- Biomira        | CETP vaccine -- Avant                   |
| cancer vaccine, PolyMASC -- Valentis       | Cetrorelix                              |
| Candida vaccine -- Corixa, Inhibitex       | Cetuximab                               |
| Canstatin -- ILEX                          | CGH 400 -- Novartis                     |
| CAP-18 -- Panorama                         | CGP 42934 -- Novartis                   |
| Cardiovascular gene therapy -- Collateral  | CGP 51901 -- Tanox                      |
| Therapeutics                               | CGRP -- Unigene                         |
| carperitide -- Suntory                     | CGS 27913 -- Novartis                   |
| Casocidin-1 -- Pharis                      | CGS 32359 -- Novartis                   |
| CAT 152 -- Cambridge Antibody Tech.        | Chagas disease vaccine -- Corixa        |
| CAT 192 -- Cambridge Antibody Tech.        | chemokines -- Immune Response           |
| CAT 213 -- Cambridge Antibody Tech.        | CHH 380 -- Novartis                     |
| Catalase -- Enzon                          | chitinase -- Genzyme, ICOS              |
| Cat-PAD -- Circassia                       | Chlamydia pneumoniae vaccine -- Antex   |
| CB 0006 -- Celltech                        | Biologics                               |
| CCK(27-32) -- Akzo Nobel                   | Chlamydia trachomatis vaccine -- Antex  |
| CCR2-64I -- NIH                            | Biologics                               |
| CD, Procept -- Paligent                    | Chlamydia vaccine -- GlaxoSmithKline    |
| CD154 gene therapy                         | Cholera vaccine CVD 103-HgR -- Swiss    |
| CD39 -- Immunex                            | Serum and Vaccine Institute Berne       |
| CD39-L2 -- Hyseq                           | Cholera vaccine CVD 112 -- Swiss Serum  |
| CD39-L4 -- Hyseq                           | and Vaccine Institute Berne             |

FIG. 28H

39/497

|                                               |                                         |
|-----------------------------------------------|-----------------------------------------|
| Cholera vaccine inactivated oral – SBL        | CRL 1605 – CytRx                        |
| Vaccin                                        | CS-560 – Sankyo                         |
| Chrysalin – Chrysalis BioTech.                | CSF – ZymoGenetics                      |
| CI-782 – Hitachi Kase                         | CSF-G – Hangzhou, Dong-A, Hanmi         |
| Ciliary neurotrophic factor – Fidia, Roche    | CSF-GM – Cangene, Hunan, LG Chem        |
| CIM project – Active Biotech                  | CSF-M – Zarix                           |
| CL 329753 – Wyeth-Ayerst                      | CT 1579 – Merck Frosst                  |
| CL22, Cobra – ML Laboratories                 | CT 1786 – Merck Frosst                  |
| Clenoliximab – IDEC                           | CT-112 <sup>Δ</sup> – BTG               |
| Clostridium difficile antibodies – Epicyte    | CTB-134L – Xenova                       |
| clotting factors – Octogene                   | CTC-111 – Kaketsuken                    |
| CMB 401 – Celltech                            | CTGF – FibroGen                         |
| CNTF -- Sigma-Tau                             | CTLA4-Ig – Bristol-Myers Squibb         |
| Cocaine abuse vaccine – Cantab,               | CTLA4-Ig gene therapy –                 |
| ImmuLogic, Scripps                            | CTP-37 – AVI BioPharma                  |
| coccidiomycosis vaccine -- Arizo              | C-type natriuretic peptide – Suntory    |
| collagen – Type I – Pharming                  | CVS 995 – Corvas Intl.                  |
| Collagen formation inhibitors – FibroGen      | CX 397 – Nikko Kyodo                    |
| Collagen/hydroxyapatite/bone growth factor    | CY 1747 – Epimmune                      |
| – Aventis Pasteur, Biopharm, Orquest          | CY 1748 -- Epimmune                     |
| collagenase -- BioSpecifics                   | Cyanovirin-N                            |
| Colorectal cancer vaccine -- Wistar Institute | Cystic fibrosis therapy -- CBR/IVAX     |
| Component B, Recombinant -- Serono            | CYT 351                                 |
| Connective tissue growth factor inhibitors -- | cytokine Traps -- Regeneron             |
| FibroGen/Taisho                               | cytokines – Enzon, Cytoclonal           |
| Contortrostatin                               | Cytomegalovirus glycoprotein vaccine -- |
| contraceptive vaccine -- Zonagen              | Chiron, Aquila Biopharmaceuticals,      |
| Contraceptive vaccine hCG                     | Aventis Pasteur, Virogenetics           |
| Contraceptive vaccine male reversible --      | Cytomegalovirus vaccine live -- Aventis |
| IMMUCON                                       | Pasteur                                 |
| Contraceptive vaccine zona pellucida --       | Cytosine deaminase gene therapy --      |
| Zonagen                                       | GlaxoSmithKline                         |
| Copper-64 labelled MAb TETA-1A3 -- NCI        | DA-3003 -- Dong-A                       |
| Coralyne                                      | DAB389interleukin-6 -- Senetek          |
| Corsevin M                                    | DAB389interleukin-7                     |
| C-peptide analogues -- Schwarz                | Daclizumab (anti-IL2R MAb) – Protein    |
| CPI-1500 – Consensus                          | Design Labs                             |
| CRF – Neurobiological Tech.                   | DAMP <sup>Δ</sup> – Incyte Genomics     |
| cRGDFV pentapeptide --                        | Daniplestim -- Pharmacia                |
| CRL 1095 – CytRx                              | darbepoetin alfa – Amgen                |
| CRL 1336 – CytRx                              | DBI-3019 – Diabetogen                   |

FIG. 281

40/497

|                                                                     |                                                                           |
|---------------------------------------------------------------------|---------------------------------------------------------------------------|
| DCC -- Genzyme                                                      | Duteplase -- Baxter Intl.                                                 |
| DDF -- Hyseq                                                        | DWP-401 -- Daewoong                                                       |
| decorin -- Integra, Telios                                          | DWP-404 -- Daewoong                                                       |
| defensins -- Large Scale Biology                                    | DWP-408 -- Daewoong                                                       |
| DEGR-VIIa                                                           | Dx 88 (Epi-KAL2) -- Dyax                                                  |
| DeImmunised antibody 3B6/22 AGEN                                    | Dx 890 (elastin inhibitors) -- Dyax                                       |
| Deimmunised anti-cancer antibodies -- Biovation/Viragen             | E coli O157 vaccine -- NIH                                                |
| Dendroamide A                                                       | E21-R -- BresaGen                                                         |
| Dengue vaccine -- Bavarian Nordic, Merck                            | Eastern equine encephalitis virus vaccine --                              |
| denileukin diftitox -- Ligand                                       | Echicetin --                                                              |
| DES-1101 -- Desmos                                                  | Echinhibin 1 --                                                           |
| desirudin -- Novartis                                               | Echistatin -- Merck                                                       |
| desmopressin -- Unigene                                             | Echitamine --                                                             |
| Desmoteplase -- Merck, Schering AG                                  | Ecromeximab -- Kyowa Hakko                                                |
| Destabilase                                                         | EC-SOD -- PPL Therapeutics                                                |
| Diabetes gene therapy -- DeveloGen, Pfizer                          | Eculizumab (5G1.1) -- Alexion                                             |
| Diabetes therapy -- Crucell                                         | EDF -- Ajinomoto                                                          |
| Diabetes type 1 vaccine -- Diamyd Therapeutics                      | EDN derivative -- NIH                                                     |
| DiaCIM -- YM BioSciences                                            | EDNA -- NIH                                                               |
| dialytic oligopeptides -- Research Corp                             | Edobacomab -- XOMA                                                        |
| Diamyd -- Diamyd Therapeutics                                       | Edrecolomab -- Centocor                                                   |
| DiaPep227 -- Pepgen                                                 | EF 5077                                                                   |
| DiavaX -- Corixa                                                    | Efalizumab -- Genentech                                                   |
| Digoxin MAb -- Glaxo                                                | EGF fusion toxin -- Seragen, Ligand                                       |
| Diphtheria tetanus pertussis-hepatitis B vaccine -- GlaxoSmithKline | EGF-P64k vaccine -- Center of Molecular Immunology                        |
| DIR therapy -- Solis Therapeutics --                                | EL 246 -- LigoCyte                                                        |
| DNase -- Genentech                                                  | elastase inhibitor -- Synergen                                            |
| Dornase alfa -- Genentech                                           | elcatonin -- Therapicon                                                   |
| Dornase alfa, inhalation -- Genentech                               | EMD 72000 -- Merck KGaA                                                   |
| Doxorubicin-anti-CEA MAb conjugate -- Immunomedics                  | Emdogain -- BIORA                                                         |
| DP-107 -- Trimeris                                                  | emfilermin -- AMRAD                                                       |
| drotrecogin alfa -- Eli Lilly                                       | Emoctakin -- Novartis                                                     |
| DTctGMCSF                                                           | enamel matrix protein -- BIORA                                            |
| DTP-polio vaccine -- Aventis Pasteur                                | Endo III -- NYU                                                           |
| DU 257-KM231 antibody conjugate -- Kyowa                            | endostatin -- EntreMed, Pharis                                            |
| dural graft matrix -- Integra                                       | Enhancins -- Micrologix                                                   |
|                                                                     | Enlimomab -- Isis Pharm.                                                  |
|                                                                     | Enoxaparin sodium -- Pharmuka                                             |
|                                                                     | enzyme linked antibody nutrient depletion therapy -- KS Biomedix Holdings |

FIG. 28J

41/497

|                                                                                                                                                                |                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Eosinophil-derived neutralizing agent – EP-51216 – Asta Medica                                                                                                 | Factor VII – Novo Nordisk, Bayer, Baxter Intl.                                         |
| EP-51389 – Asta Medica                                                                                                                                         | Factor VIIa – PPL Therapeutics, ZymoGenetics                                           |
| EPH family ligands – Regeneron                                                                                                                                 | Factor VIII – Bayer Genentech, Beaufour-Ipsen, CLB, Inex, Octagen, Pharmacia, Pharming |
| Epidermal growth factor – Hitachi Kasei, Johnson & Johnson                                                                                                     | Factor VIII – PEGylated – Bayer                                                        |
| Epidermal growth factor fusion toxin – Senetek                                                                                                                 | Factor VIII fragments – Pharmacia                                                      |
| Epidermal growth factor-genistein – EPI-HNE-4 – Dyax                                                                                                           | Factor VIII gene therapy – Targeted Genetics                                           |
| EPI-KAL2 – Dyax                                                                                                                                                | Factor VIII sucrose formulation – Bayer, Genentech                                     |
| Epoetin-alfa – Amgen, Dragon Pharmaceuticals, Nanjing Huaxin                                                                                                   | Factor VIII-2 – Bayer                                                                  |
| Epratuzumab – Immunomedics                                                                                                                                     | Factor VIII-3 – Bayer                                                                  |
| Epstein-Barr virus vaccine – Aviron/SmithKline Beecham, Bioresearch                                                                                            | Factor Xa inhibitors – Merck, Novo Nordisk, Mochida                                    |
| Eptacog alfa – Novo Nordisk                                                                                                                                    | Factor XIII – ZymoGenetics                                                             |
| Eptifibatide – COR Therapeutics                                                                                                                                | Factors VIII and IX gene therapy – Genetics Institute/Targeted Genetics                |
| erb-38 – Erlizumab – Genentech                                                                                                                                 | Famoxin – Genset                                                                       |
| erythropoietin – Alkermes, ProLease, Dong-A, Elanex, Genetics Institute, LG Chem, Protein Sciences, Serono, Snow Brand, SRC VB VECTOR, Transkaryotic Therapies | Fas (delta) TM protein – LXR BioTech.                                                  |
| Erythropoietin Beta – Hoffman La Roche                                                                                                                         | Fas TR – Human Genome Sciences                                                         |
| Erythropoietin/Epoetin alfa – Chugai                                                                                                                           | Felvizumab – Scotgen                                                                   |
| Escherichia coli vaccine – North American Vaccine, SBL Vaccin, Swiss Serum and Vaccine Institute Berne                                                         | FFR-VIIa – Novo Nordisk                                                                |
| etanercept – Immunex                                                                                                                                           | FG-001 – F-Gene                                                                        |
| examorelin – Mediolanum                                                                                                                                        | FG-002 – F-Gene                                                                        |
| Exendin 4 – Amylin                                                                                                                                             | FG-004 – F-Gene                                                                        |
| exonuclease VII                                                                                                                                                | FG-005 – F-Gene                                                                        |
| F 105 – Centocor                                                                                                                                               | FGF + fibrin – Repair                                                                  |
| F-992 – Fornix                                                                                                                                                 | Fibrimage – Bio-Tech. General                                                          |
| Factor IX – Alpha Therapeutics, Welfide Corp., CSL, enetics Institute/AHP, Pharmacia, PPL Therapeutics                                                         | fibrin-binding peptides – ISIS Innovation                                              |
| Factor IX gene therapy – Cell Genesys                                                                                                                          | fibrinogen – PPL Therapeutics, Pharming                                                |
|                                                                                                                                                                | fibroblast growth factor – Chiron, NYU, Ramot, ZymoGenetics                            |
|                                                                                                                                                                | fibrolase conjugate – Schering AG                                                      |
|                                                                                                                                                                | Filgrastim – Amgen                                                                     |
|                                                                                                                                                                | filgrastim – PDA modified – Xencor                                                     |
|                                                                                                                                                                | FLT-3 ligand – Immunex                                                                 |
|                                                                                                                                                                | FN18 CRM9 –                                                                            |

FIG. 28K

42/497

|                                                                          |                                                                           |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
| follistatin -- Biotech Australia, Human Therapeutics                     | glutamate decarboxylase -- Genzyme Transgenics                            |
| follitropin alfa -- Alkermes, ProLease, PowderJect, Serono, Akzo Nobel   | Glycoprotein S3 -- Kureha                                                 |
| Follitropin Beta -- Bayer, Organon                                       | GM-CSF -- Immunex                                                         |
| FP 59                                                                    | GM-CSF tumour vaccine -- PowderJect                                       |
| FSH -- Ferring                                                           | GnRH immunotherapeutic -- Protherics                                      |
| FSH + LH -- Ferring                                                      | Goserelin (LhRH antagonist) -- AstraZeneca                                |
| F-spondin -- CeNeS                                                       | gp75 antigen -- ImClone                                                   |
| fusion protein delivery system -- UAB Research Foundation                | gp96 -- Antigenics                                                        |
| fusion toxins -- Boston Life Sciences                                    | GPI 0100 -- Galenica                                                      |
| G 5598 -- Genentech                                                      | GR 4991W93 -- GlaxoSmithKline                                             |
| GA-II -- Transkaryotic Therapies                                         | Granulocyte colony-stimulating factor -- Dong-A                           |
| Gamma-interferon analogues -- SRC VB VECTOR                              | Granulocyte colony-stimulating factor conjugate                           |
| Ganirelix -- Roche                                                       | grass allergy therapy -- Dynavax                                          |
| gastric lipase -- Meristem                                               | GRF1-44 -- ICN                                                            |
| Gavilimomab --                                                           | Growth Factor -- Chiron, Atrigel, Atrix, Innogenetics, ZymoGenetics, Novo |
| G-CSF -- Amgen, SRC VB VECTOR                                            | growth factor peptides -- Biotherapeutics                                 |
| GDF-1 -- CeNeS                                                           | growth hormone -- LG Chem                                                 |
| GDF-5 -- Biopharm                                                        | growth hormone, Recombinant human -- Serono                               |
| GDNF (glial derived neurotrophic factor) -- Amgen                        | GT 4086 -- Gliatech                                                       |
| gelsolin -- Biogen                                                       | GW 353430 -- GlaxoSmithKline                                              |
| Gemtuzumab ozogamicin -- Celltech                                        | GW-278884 -- GlaxoSmithKline                                              |
| Gene-activated epoetin-alfa -- Aventis Pharma -- Transkaryotic Therapies | H 11 -- Viventia Biotech                                                  |
| Glanzmann thrombasthenia gene therapy --                                 | H5N1 influenza A virus vaccine -- Protein Sciences                        |
| Glatiramer acetate -- Yeda                                               | haemoglobin -- Biopure                                                    |
| glial growth factor 2 -- CeNeS                                           | haemoglobin 3011, Recombinant -- Baxter Healthcare                        |
| GLP-1 -- Amylin, Suntory, TheraTech, Watson                              | haemoglobin crosumaril -- Baxter Intl.                                    |
| GLP-1 peptide analogues -- Zealand Pharmaceuticals                       | haemoglobin stabilized -- Ajinomoto                                       |
| glucagon -- Eli Lilly, ZymoGenetics                                      | haemoglobin, recombinant -- Apex                                          |
| Glucagon-like peptide-1 7-36 amide -- Suntory                            | HAF -- Immune Response                                                    |
| Glucogen-like peptide -- Amylin                                          | Hantavirus vaccine                                                        |
| Glucocerebrosidase -- Genzyme                                            | HB 19                                                                     |
|                                                                          | HBNF -- Regeneron                                                         |
|                                                                          | HCC-1 -- Pharis                                                           |
|                                                                          | hCG -- Milkhaus                                                           |

FIG. 28L



43/497

|                                               |                                            |
|-----------------------------------------------|--------------------------------------------|
| hCG vaccine -- Zonagen                        | Herpes simplex glycoprotein DNA vaccine -- |
| HE-317 -- Hollis-Eden Pharmaceuticals         | Merck, Wyeth-Lederle Vaccines-Malvern,     |
| Heat shock protein cancer and influenza       | Genentech, GlaxoSmithKline, Chiron,        |
| vaccines -- StressGen                         | Takeda                                     |
| Helicobacter pylori vaccine -- Acambis,       | Herpes simplex vaccine -- Cantab           |
| AstraZeneca/CSL, Chiron, Provalis             | Pharmaceuticals, CEL-SCI, Henderson        |
| Helistat-G -- GalaGen                         | Morley                                     |
| Hemolink -- Hemosol                           | Herpes simplex vaccine live -- ImClone     |
| hepapoietin -- Snow Brand                     | Systems/Wyeth-Lederle, Aventis Pasteur     |
| heparanase -- InSight                         | HGF derivatives -- Dompe                   |
| heparinase I -- Ibex                          | hIAPP vaccine -- Crucell                   |
| heparinase III -- Ibex                        | Hib-hepatitis B vaccine -- Aventis Pasteur |
| Hepatitis A vaccine -- American Biogenetic    | HIC 1                                      |
| Sciences                                      | HIP -- Altachem                            |
| Hepatitis A vaccine inactivated               | Hirudins -- Biopharma, Cangene, Dongkook,  |
| Hepatitis A vaccine Nothav -- Chiron          | Japan Energy Corporation, Pharmacia        |
| Hepatitis A-hepatitis B vaccine --            | Corporation, SIR International, Sanofi-    |
| GlaxoSmithKline                               | Synthelabo, Sotragene, Rhein Biotech       |
| hepatitis B therapy -- Tripep                 | HIV edible vaccine -- ProdiGene            |
| Hepatitis B vaccine -- Amgen, Chiron SpA,     | HIV gp120 vaccine -- Chiron, Ajinomoto,    |
| Meiji Milk, NIS, Prodeva, PowderJect,         | GlaxoSmithKline, ID Vaccine, Progenics,    |
| Rhein Biotech                                 | VaxGen                                     |
| Hepatitis B vaccine recombinant -- Evans      | HIV gp120 vaccine gene therapy --          |
| Vaccines, Epitex Combiotech, Genentech,       | HIV gp160 DNA vaccine -- PowderJect,       |
| MedImmune, Merck Sharp & Dohme,               | Aventis Pasteur, Oncogen, Hyland           |
| Rhein Biotech, Shantha Biotechnics,           | Immuno, Protein Sciences                   |
| Vector, Yeda                                  | HIV gp41 vaccine -- Panacos                |
| Hepatitis B vaccine recombinant TGP 943 --    | HIV HGP-30W vaccine -- CEL-SCI             |
| Takeda                                        | HIV immune globulin -- Abbott, Chiron      |
| Hepatitis C vaccine -- Bavarian Nordic,       | HIV peptides -- American Home Products     |
| Chiron, Innogenetics Acambis,                 | HIV vaccine -- Applied bioTech., Axis      |
| Hepatitis D vaccine -- Chiron Vaccines        | Genetics, Biogen, Bristol-Myers Squibb,    |
| Hepatitis E vaccine recombinant --            | Genentech, Korea Green Cross, NIS,         |
| Genelabs/GlaxoSmithKline, Novavax             | Oncogen, Protein Sciences Corporation,     |
| hepatocyte growth factor -- Panorama,         | Terumo, Tonen Corporation, Wyeth-          |
| Sosei                                         | Ayerst, Wyeth-Lederle Vaccines-Malvern,    |
| hepatocyte growth factor kringle fragments -- | Advanced BioScience Laboratories,          |
| - EntreMed                                    | Bavarian Nordic, Bavarian Nordic/Statens   |
| Her-2/Neu peptides -- Corixa                  | Serum Institute, GeneCure, Immune          |
|                                               | Response, Progenics, Therion Biologics,    |
|                                               | United Biomedical, Chiron                  |

FIG. 28M

44/497

|                                          |                                            |
|------------------------------------------|--------------------------------------------|
| HIV vaccine vCP1433 -- Aventis Pasteur   | Human monoclonal antibodies --             |
| HIV vaccine vCP1452 -- Aventis Pasteur   | Medarex/Northwest Biotherapeutics,         |
| HIV vaccine vCP205 -- Aventis Pasteur    | Medarex/Seattle Genetics                   |
| HL-9 -- American BioScience              | human netrin-1 -- Exelixis                 |
| HM-9239 -- Cytran                        | human papillomavirus antibodies -- Epicyte |
| HML-103 -- Hemosol                       | Human papillomavirus vaccine -- Biotech    |
| HML-104 -- Hemosol                       | Australia, IDEC, StressGen                 |
| HML-105 -- Hemosol                       | Human papillomavirus vaccine MEDI 501 --   |
| HML-109 -- Hemosol                       | MedImmune/GlaxoSmithKline                  |
| HML-110 -- Hemosol                       | Human papillomavirus vaccine MEDI          |
| HML-121 -- Hemosol                       | 503/MEDI 504 --                            |
| hNLP -- Pharis                           | MedImmune/GlaxoSmithKline                  |
| Hookworm vaccine                         | Human papillomavirus vaccine TA-CIN --     |
| host-vector vaccines -- Henogen          | Cantab Pharmaceuticals                     |
| HPM 1 -- Chugai                          | Human papillomavirus vaccine TA-HPV --     |
| HPV vaccine -- MediGene                  | Cantab Pharmaceuticals                     |
| HSA -- Meristem                          | Human papillomavirus vaccine TH-GW --      |
| HSF -- StressGen                         | Cantab/GlaxoSmithKline                     |
| HSP carriers -- Weizmann, Yeda, Peptor   | human polyclonal antibodies -- Biosite/Eos |
| HSPPC-70 -- Antigenics                   | BioTech./ Medarex                          |
| HSPPC-96, pathogen-derived -- Antigenics | human type II anti factor VIII monoclonal  |
| HSV 863 -- Novartis                      | antibodies -- ThromboGenics                |
| HTLV-I DNA vaccine                       | humanised anti glycoprotein Ib murine      |
| HTLV-I vaccine                           | monoclonal antibodies -- ThromboGenics     |
| HTLV-II vaccine -- Access                | HumaRAD -- Intracell                       |
| HU 901 -- Tanox                          | HuMax EGFR -- Genmab                       |
| Hu23F2G -- ICOS                          | HuMax-CD4 -- Medarex                       |
| HuHMFG1                                  | HuMax-IL15 -- Genmab                       |
| HumaLYM -- Intracell                     | HYB 190 -- Hybridon                        |
| Human krebs statika -- Yamanouchi        | HYB 676 -- Hybridon                        |
| human monoclonal antibodies --           | I-125 MAb A33 -- Celltech                  |
| Abgenix/Biogen, Abgenix/ Corixa,         | Ibritumomab tiuxetan -- IDEC               |
| Abgenix/Immunex, Abgenix/Lexicon,        | IBT-9401 -- Ibex                           |
| Abgenix/ Pfizer, Athersys/Medarex,       | IBT-9402 -- Ibex                           |
| Biogen/MorphoSys, CAT/Searle,            | IC 14 -- ICOS                              |
| Centocor/Medarex, Corixa/Kirin Brewery,  | Idarubicin anti-Ly-2.1 --                  |
| Corixa/Medarex, Eos BioTech./Medarex,    | IDEC 114 -- IDEC                           |
| Eos/Xenerex, Exelixis/Protein Design     | IDEC 131 -- IDEC                           |
| Labs, ImmunoGen/ Raven, Medarex/         | IDEC 152 -- IDEC                           |
| B.Twelve, MorphoSys/ImmunoGen, XTL       | IDM 1 -- IDM                               |
| Biopharmaceuticals/Dyax,                 | IDPS -- Hollis-Eden Pharmaceuticals        |

FIG. 28N

45/497

|                                                              |                                                                                                                                             |
|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| iduronate-2-sulfatase -- Transkaryotic Therapies             | insulin -- AutoImmune, Altea, Biobras, BioSante, Bio-Tech. General, Chong Kun Dang, Emisphere, Flamel, Provalis, Rhein Biotech, TranXenoGen |
| IGF/IBP-2-13 -- Pharis                                       | insulin (bovine) -- Novartis                                                                                                                |
| IGN-101 -- Igeneon                                           | insulin analogue -- Eli Lilly                                                                                                               |
| IK HIR02 -- Iketon                                           | Insulin Aspart -- Novo Nordisk                                                                                                              |
| IL-11 -- Genetics Institute/AHP                              | insulin detemir -- Novo Nordisk                                                                                                             |
| IL-13-PE38 -- NeoPharm                                       | insulin glargine -- Aventis                                                                                                                 |
| IL-17 receptor -- Immunex                                    | insulin inhaled -- Inhale Therapeutics Systems, Alkermes                                                                                    |
| IL-18BP -- Yeda                                              | insulin oral -- Inovax                                                                                                                      |
| IL-1Hy1 -- Hyseq                                             | insulin, AeroDose -- AeroGen                                                                                                                |
| IL-1 $\beta$ -- Celltech                                     | insulin, AERx -- Aradigm                                                                                                                    |
| IL-1 $\beta$ adjuvant -- Celltech                            | insulin, BEODAS -- Elan                                                                                                                     |
| IL-2 -- Chiron                                               | insulin, Biphax -- Helix                                                                                                                    |
| IL-2 + IL-12 -- Hoffman La-Roche                             | insulin, buccal -- Generex                                                                                                                  |
| IL-6/sIL-6R fusion -- Hadasit                                | insulin, I2R -- Flemington                                                                                                                  |
| IL-6R derivative -- Tosoh                                    | insulin, intranasal -- Bentley                                                                                                              |
| IL-7-Dap 389 fusion toxin -- Ligand                          | insulin, oral -- Nobex, Unigene                                                                                                             |
| IM-862 -- Cytran                                             | insulin, Orasome -- Endorex                                                                                                                 |
| IMC-1C11 -- ImClone                                          | insulin, ProMaxx -- Epic                                                                                                                    |
| imiglucerase -- Genzyme                                      | insulin, Quadrant -- Elan                                                                                                                   |
| Immune globulin intravenous (human) -- Hoffman La Roche      | insulin, recombinant -- Aventis                                                                                                             |
| immune privilege factor -- Proneuron                         | insulin, Spiros -- Elan                                                                                                                     |
| Immunocal -- Immunotec                                       | insulin, Transfersome -- IDEA                                                                                                               |
| Immunogene therapy -- Briana Bio-Tech                        | insulin, Zymo, recombinant -- Novo Nordisk                                                                                                  |
| Immunoliposomal 5-fluorodeoxyuridine-dipalmitate --          | insulinotropin -- Scios                                                                                                                     |
| immunosuppressant vaccine -- Aixie                           | Insulysin gene therapy --                                                                                                                   |
| immunotoxin -- Antisoma, NIH                                 | integrin antagonists -- Merck                                                                                                               |
| ImmuRAIT-Re-188 -- Immunomedics                              | interferon (Alpha2) -- SRC VB VECTOR, Viragen, Dong-A, Hoffman La-Roche, Genentech                                                          |
| imreg-1 -- Imreg                                             | interferon -- BioMedicines, Human Genome Sciences                                                                                           |
| infertility -- Johnson & Johnson, E-TRANS                    | interferon (Alfa-n3) -- Interferon Sciences Intl.                                                                                           |
| Infliximab -- Centocor                                       | interferon (Alpha), Biphax -- Helix                                                                                                         |
| Influenza virus vaccine -- Aventis Pasteur, Protein Sciences |                                                                                                                                             |
| inhibin -- Biotech Australia, Human Therapeutics             |                                                                                                                                             |
| Inhibitory G protein gene therapy                            |                                                                                                                                             |
| INKP-2001 -- InKine                                          |                                                                                                                                             |
| Inolimomab -- Diaclone                                       |                                                                                                                                             |

FIG. 280

46/497

|                                            |                                              |
|--------------------------------------------|----------------------------------------------|
| interferon (Alpha)—Amgen, BioNative,       | IL-2/ diphtheria toxin — Ligand              |
| Novartis, Genzyme Transgenics,             | Interleukin-3 — Cangene                      |
| Hayashibara, Inhale Therapeutics           | Interleukin-4 — Immunology Ventures,         |
| Systems, Medusa, Flamel, Dong-A,           | Sanofi Winthrop, Schering-Plough,            |
| GeneTrol, Nastech, Shantha,                | Immunex/ Sanofi Winthrop, Bayer, Ono         |
| Wassermann, LG Chem, Sumitomo,             | interleukin-4 + TNF-Alpha — NIH              |
| Aventis, Behring EGIS, Pepgen, Servier,    | interleukin-4 agonist — Bayer                |
| Rhein Biotech,                             | interleukin-4 fusion toxin — Ligand          |
| interferon (Alpha2A)                       | Interleukin-4 receptor — Immunex, Immun      |
| interferon (Alpha2B) — Enzon, Schering-    | Interleukin-6 — Ajinomoto, Cangene, Yeda,    |
| Plough, Biogen, IDEA                       | Genetics Institute, Novartis                 |
| interferon (Alpha-N1) — GlaxoSmithKline    | interleukin-6 fusion protein                 |
| interferon (beta) — Rentschler, GeneTrol,  | interleukin-6 fusion toxin — Ligand, Serono  |
| Meristem, Rhein Biotech, Toray, Yeda,      | interleukin-7 — IC Innovations               |
| Dalichi, Mochida                           | interleukin-7 receptor — Immunex             |
| interferon (Beta1A) — Serono, Biogen       | interleukin-8 antagonists — Kyowa            |
| interferon (beta1A), inhale — Biogen       | Hakko/Millennium/Pfizer                      |
| interferon (B1b) — Chiron                  | interleukin-9 antagonists — Genaera          |
| interferon (tau) — Pepgen                  | Interleukin-10 — DNAX, Schering-Plough       |
| Interferon alfacon-1 — Amgen               | Interleukin-10 gene therapy —                |
| Interferon alpha-2a vaccine                | interleukin-12 — Genetics Institute, Hoffman |
| Interferon Beta 1b — Schering/Chiron,      | La-Roche                                     |
| InterMune                                  | interleukin-13 — Sanofi                      |
| Interferon Gamma — Boehringer Ingelheim,   | interleukin-13 antagonists — AMRAD           |
| Sheffield, Rentschler, Hayashibara         | Interleukin-13-PE38QQR                       |
| interferon receptor, Type I — Serono       | Interleukin-15 — Immunex                     |
| interferon(Gamma1B) — Genentech            | interleukin-16 — Research Corp               |
| Interferon-alpha-2b + ribavirin — Biogen,  | interleukin-18 — GlaxoSmithKline             |
| ICN                                        | Interleukin-18 binding protein — Serono      |
| Interferon-alpha-2b gene therapy —         | lor-P3 — Center of Molecular Immunology      |
| Schering-Plough                            | IP-10 — NIH                                  |
| Interferon-con1 gene therapy —             | IPF — Metabolex                              |
| interleukin-1 antagonists — Dompe          | IR-501 — Immune Response                     |
| Interleukin-1 receptor antagonist — Abbott | ISIS 9125 — Isis Pharmaceuticals             |
| Bioresearch, Pharmacia                     | ISURF No. 1554 — Millennium                  |
| Interleukin-1 receptor type I — Immunex    | ISURF No. 1866 — Iowa State Univer.          |
| interleukin-1 receptor Type II — Immunex   | ITF-1697 — Italfarmaco                       |
| Interleukin-1 trap — Regeneron             | IxC 162 — Ixion                              |
| Interleukin-1-alpha — Immunex/Roche        | J 695 — Cambridge Antibody Tech.,            |
| interleukin-2 — SRC VB VECTOR,             | Genetics Inst., Knoll                        |
| Ajinomoto, Biomira, Chiron                 | Jagged + FGF — Repair                        |

FIG. 28P

47/497

|                                                |                                                                         |
|------------------------------------------------|-------------------------------------------------------------------------|
| JKC-362 -- Phoenix Pharmaceuticals             | leptin, 2nd-generation -- Amgen                                         |
| JTP-2942 -- Japan Tobacco                      | leridistim -- Pharmacia                                                 |
| Juman monoclonal antibodies -- Medarex/Raven   | leuprolide, ProMaxx -- Epic                                             |
| K02 -- Axy's Pharmaceuticals                   | leuprorelin, oral -- Unigene                                            |
| Kelliximab -- IDEC                             | LeuTech -- Papatin                                                      |
| Keyhole limpet haemocyanin                     | LEX 032 -- SuperGen                                                     |
| KGF -- Amgen                                   | LiDEPT -- Novartis                                                      |
| KM 871 -- Kyowa                                | Lintuzumab (anti-CD33 MAb) -- Protein Design Labs                       |
| KPI 135 -- Scios                               | lipase -- Altus Biologics                                               |
| KPI-022 -- Scios                               | lipid A vaccine -- EntreMed                                             |
| Kringle 5                                      | lipid-linked anchor Tech. -- ICRT, ID Biomedical                        |
| KSB 304                                        | liposome-CD4 Tech. -- Sheffield                                         |
| KSB-201 -- KS Biomedix                         | Listeria monocytogenes vaccine                                          |
| L 696418 -- Merck                              | LMB 1                                                                   |
| L 703801 -- Merck                              | LMB 7                                                                   |
| L1 -- Acorda                                   | LMB 9 -- Battelle Memorial Institute, NIH                               |
| L-761191 -- Merck                              | LM-CD45 -- Cantab Pharmaceuticals                                       |
| lactoferrin -- Meristem, Pharming, Agennix     | lovastatin -- Merck                                                     |
| lactoferrin cardio -- Pharming                 | LSA-3                                                                   |
| LAG-3 -- Serono                                | LT- $\beta$ receptor -- Biogen                                          |
| LAIT -- GEMMA                                  | lung cancer vaccine -- Corixa                                           |
| LAK cell cytotoxin -- Arizona                  | lusupultide -- Scios                                                    |
| lamellarins -- PharmaMar/University of Malaga  | L-Vax -- AVAX                                                           |
| laminin A peptides -- NIH                      | LY 355455 -- Eli Lilly                                                  |
| lanotepase -- Genetics Institute               | LY 366405 -- Eli Lilly                                                  |
| laronidase -- BioMarin                         | LY-355101 -- Eli Lilly                                                  |
| Lassa fever vaccine                            | Lyme disease DNA vaccine -- Vical/Aventis Pasteur                       |
| LCAT -- NIH                                    | Lyme disease vaccine -- Aquila                                          |
| LDP 01 -- Millennium                           | Biopharmaceuticals, Aventis, Pasteur, Symbicom, GlaxoSmithKline, Hyland |
| LDP 02 -- Millennium                           | Immuno, MedImmune                                                       |
| Lecithinized superoxide dismutase -- Seikagaku | Lymphocytic choriomeningitis virus vaccine                              |
| LeIF adjuvant -- Corixa                        | lymphoma vaccine -- Biomira, Genitope                                   |
| leishmaniasis vaccine -- Corixa                | LYP18                                                                   |
| lenercept -- Hoffman La-Roche                  | lys plasminogen, recombinant                                            |
| Lenograstim -- Aventis, Chugai                 | Lysosomal storage disease gene therapy -- Avigen                        |
| lepirudin -- Aventis                           | lysostaphin -- Nutrition 21                                             |
| leptin -- Amgen, IC Innovations                |                                                                         |
| Leptin gene therapy -- Chiron Corporation      |                                                                         |

FIG. 28Q

48/497

|                                        |                                           |
|----------------------------------------|-------------------------------------------|
| M 23 -- Gruenenthal                    | MEDI 507 -- BioTransplant                 |
| M1 monoclonal antibodies -- Acorda     | melanin concentrating hormone --          |
| Therapeutics                           | Neurocrine Biosciences                    |
| MA 16N7C2 -- Corvas Intl.              | melanocortins -- OMRF                     |
| malaria vaccine -- GlaxoSmithKline,    | Melanoma monoclonal antibodies -- Viragen |
| AdProTech, Antigenics, Apovia, Aventis | melanoma vaccine -- GlaxoSmithKline,      |
| Pasteur, Axis Genetics, Behringwerke,  | Akzo Nobel, Avant, Aventis Pasteur,       |
| CDCP, Chiron Vaccines, Genzyme         | Bavarian Nordic, Biovector, CancerVax,    |
| Transgenics, Hawaii, MedImmune, NIH,   | Genzyme Molecular Oncology, Humbolt,      |
| NYU, Oxon, Roche/Saramane, Biotech     | ImClone Systems, Memorial, NYU, Oxon      |
| Australia, Rx Tech                     | Melanoma vaccine Magevac -- Therion       |
| Malaria vaccine CDC/NIIMALVAC-1        | memory enhancers -- Scios                 |
| malaria vaccine, multicomponent        | meningococcal B vaccine -- Chiron         |
| mammaglobin -- Corixa                  | meningococcal vaccine -- CAMR             |
| mammastatin -- Biotherapeutics         | Meningococcal vaccine group B conjugate - |
| mannan-binding lectin -- NatImmu       | - North American Vaccine                  |
| mannan-MUC1 -- Psiron                  | Meningococcal vaccine group B             |
| MAP 30                                 | recombinant -- BioChem Vaccines,          |
| Marinovir -- Phytera                   | Microscience                              |
| MARstem -- Maret                       | Meningococcal vaccine group Y conjugate - |
| MB-015 -- Mochida                      | - North American Vaccine                  |
| MBP -- ImmuLogic                       | Meningococcal vaccine groups A B and C    |
| MCI-028 -- Mitsubishi-Tokyo            | conjugate -- North American Vaccine       |
| MCIF -- Human Genome Sciences          | Mepolizumab -- GlaxoSmithKline            |
| MDC -- Advanced BioScience -- Akzo     | Metastatin -- EntreMed, Takeda            |
| Nobel, ICOS                            | Met-CKB7 -- Human Genome Sciences         |
| MDX 11 -- Medarex                      | met-enkephalin -- TNI                     |
| MDX 210 -- Medarex                     | METH-1 -- Human Genome Sciences           |
| MDX 22 -- Medarex                      | methioninase -- AntiCancer                |
| MDX 22                                 | Methionine lyase gene therapy --          |
| MDX 240 -- Medarex                     | AntiCancer                                |
| MDX 33                                 | Met-RANTES -- Genexa Biomedical,          |
| MDX 44 -- Medarex                      | Serono                                    |
| MDX 447 -- Medarex                     | Metreleptin                               |
| MDX H210 -- Medarex                    | Microtubule inhibitor MAb                 |
| MDX RA -- Houston BioTech., Medarex    | Immunogen/Abgenix                         |
| ME-104 -- Pharmexa                     | MGDF -- Kirin                             |
| Measles vaccine                        | MGV -- Progenics                          |
| Mecasemin -- Cephalon/Chiron, Chiron   | micrin -- Endocrine                       |
| MEDI 488 -- MedImmune                  | microplasmin -- ThromboGenics             |
| MEDI 500                               | MIF -- Genetics Institute                 |

FIG. 28R

49/497

|                                                                                                                       |                                                                 |
|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| migration inhibitory factor -- NIH                                                                                    | MAB 45-2D9- -- haematoporphyrin conjugate                       |
| Mim CD4.1 -- Xycte Therapies                                                                                          | MAB 4B4                                                         |
| mirostipen -- Human Genome Sciences                                                                                   | MAB 4E3-CPA conjugate -- BCM Oncologia                          |
| Mitumomab (BEC-2) -- ImClone Systems, Merck KGaA                                                                      | MAB 4E3-daunorubicin conjugate                                  |
| MK 852 -- Merck                                                                                                       | MAB 50-6                                                        |
| MLN 1202 (Anti-CCR2 monoclonal antibody) -- Millenium Pharmaceuticals                                                 | MAB 50-61A -- Institut Pasteur                                  |
| Mobenakin -- NIS                                                                                                      | MAB 5A8 -- Biogen                                               |
| molgramostim -- Genetics Institute, Novartis                                                                          | MAB 791T/36-methotrexate conjugate                              |
| monoclonal antibodies -- Abgenix/Celltech, Immusol/ Medarex, Viragen/ Roslin Institute, Cambridge Antibody Tech./Elan | MAB 7c11.e8                                                     |
| MAB 108 --                                                                                                            | MAB 7E11 C5-selenocystamine conjugate                           |
| MAB 10D5 --                                                                                                           | MAB 93KA9 -- Novartis                                           |
| MAB 14.18-interleukin-2 immunocytokine -- Lexigen                                                                     | MAB A5B7-cisplatin conjugate -- Biodynamics Research, Pharmacia |
| MAB 14G2a --                                                                                                          | MAB A5B7-I-131                                                  |
| MAB 15A10 --                                                                                                          | MAB A7                                                          |
| MAB 170 -- Biomira                                                                                                    | MAB A717 -- Exocell                                             |
| MAB 177Lu CC49 --                                                                                                     | MAB A7-zinostatin conjugate                                     |
| MAB 17F9                                                                                                              | MAB ABX-RB2 -- Abgenix                                          |
| MAB 1D7                                                                                                               | MAB ACA 11                                                      |
| MAB 1F7 -- Immune Network                                                                                             | MAB AFP-I-131 -- Immunomedics                                   |
| MAB 1H10-doxorubicin conjugate                                                                                        | MAB AP1                                                         |
| MAB 26-2F                                                                                                             | MAB AZ1                                                         |
| MAB 2A11                                                                                                              | MAB B3-LysPE40 conjugate                                        |
| MAB 2E1 -- RW Johnson                                                                                                 | MAB B4 -- United Biomedical                                     |
| MAB 2F5                                                                                                               | MAB B43 Genistein-conjugate                                     |
| MAB 31.1 -- International BioImmune Systems                                                                           | MAB B43.13-Tc-99m -- Biomira                                    |
| MAB 32 -- Cambridge Antibody Tech., Peptech                                                                           | MAB B43-PAP conjugate                                           |
| MAB 323A3 -- Centocor                                                                                                 | MAB B4G7-gelonin conjugate                                      |
| MAB 3C5                                                                                                               | MAB BCM 43-daunorubicin conjugate -- BCM Oncologia              |
| MAB 3F12                                                                                                              | MAB BIS-1                                                       |
| MAB 3F8                                                                                                               | MAB BMS 181170 -- Bristol-Myers Squibb                          |
| MAB 42/6                                                                                                              | MAB BR55-2                                                      |
| MAB 425 -- Merck KGaA                                                                                                 | MAB BW494                                                       |
| MAB 447-52D -- Merck Sharp & Dohme                                                                                    | MAB C 242-DM1 conjugate -- ImmunoGen                            |
|                                                                                                                       | MAB C242-PE conjugate                                           |
|                                                                                                                       | MAB c30-6                                                       |
|                                                                                                                       | MAB CA208-cytorhodin-S conjugate -- Hoechst Japan               |
|                                                                                                                       | MAB CC49 -- Enzon                                               |

FIG. 28S

50/497

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| MAb ch14.18 --                          | MAb LL2-I-131 -- Immunomedics           |
| MAb CH14.18-GM-CSF fusion protein --    | MAb LL2-Y-90                            |
| Lexigen                                 | MAb LS2D617 -- Hybritech                |
| MAb chCE7                               | MAb LYM-1-gelonin conjugate             |
| MAb CI-137 -- AMRAD                     | MAb LYM-1-I-131                         |
| MAb cisplatin conjugate                 | MAb LYM-1-Y-90                          |
| MAb CLB-CD19                            | MAb LYM-2 -- Peregrine                  |
| MAb CLB-CD19v                           | MAb M195                                |
| MAb CLL-1 -- Peregrine                  | MAb M195-bismuth 213 conjugate --       |
| MAb CLL-1-GM-CSF conjugate              | Protein Design Labs                     |
| MAb CLL-1-IL-2 conjugate -- Peregrine   | MAb M195-gelonin conjugate              |
| MAb CLN IgG -- doxorubicin conjugates   | MAb M195-I-131                          |
| MAb conjugates -- Tanox                 | MAb M195-Y-90                           |
| MAb D612                                | MAb MA 33H1 -- Sanofi                   |
| MAb Dal B02                             | MAb MAD11                               |
| MAb DC101 -- ImClone                    | MAb MGB2                                |
| MAb EA 1 --                             | MAb MINT5                               |
| MAb EC708 -- Biovation                  | MAb MK2-23                              |
| MAb EP-5C7 -- Protein Design Labs       | MAb MOC31 ETA(252-613) conjugate        |
| MAb ERIC-1 -- ICRT                      | MAb MOC-31-In-111                       |
| MAb F105 gene therapy                   | MAb MOC-31-PE conjugate                 |
| MAb FC 2.15                             | MAb MR6 --                              |
| MAb G250 -- Centocor                    | MAb MRK-16 -- Aventis Pasteur           |
| MAb GA6                                 | MAb MS11G6                              |
| MAb GA733                               | MAb MX-DTPA BrE-3                       |
| MAb Gliomab-H -- Viventia Biotech       | MAb MY9                                 |
| MAb HB2-saporin conjugate               | MAb Nd2 -- Tosoh                        |
| MAb HD 37 --                            | MAb NG-1 -- Hygeia                      |
| MAb HD37-ricin chain-A conjugate        | MAb NM01 -- Nissin Food                 |
| MAb HNK20 -- Acambis                    | MAb OC 125                              |
| MAb huN901-DM1 conjugate --             | MAb OC 125-CMA conjugate                |
| ImmunoGen                               | MAb OKI-1 -- Ortho-McNeil               |
| MAb I-131 CC49 -- Corixa                | MAb OX52 -- Bioproducts for Science     |
| MAb ICO25                               | MAb PMA5                                |
| MAb ICR12-CPG2 conjugate                | MAb PR1                                 |
| MAb ICR-62                              | MAb prost 30                            |
| MAb IRac-ricin A conjugate              | MAb R-24                                |
| MAb K1                                  | MAb R-24 $\alpha$ Human GD3 -- Celltech |
| MAb KS1-4-methotrexate conjugate        | MAb RFB4-ricin chain A conjugate        |
| MAb L6 -- Bristol-Myers Squibb, Oncogen | MAb RFT5-ricin chain A conjugate        |
| MAb LiCO 16-88                          | MAb SC 1                                |

FIG. 28T



51/497

|                                        |                                            |
|----------------------------------------|--------------------------------------------|
| MAB SM-3 -- ICRT                       | Muc-1 vaccine -- Corixa                    |
| MAB SMART 1D10 -- Protein Design Labs  | mucosal tolerance -- Aberdeen              |
| MAB SMART ABL 364 -- Novartis          | mullerian inhibiting subst                 |
| MAB SN6f                               | muplestim -- Genetics Institute, Novartis, |
| MAB SN6f-deglycosylated ricin A chain  | DSM Anti-Infectives                        |
| conjugate --                           | murine MAB -- KS Biomedix                  |
| MAB SN6j                               | Mutant somatropin -- JCR Pharmaceutical    |
| MAB SN7-ricin chain A conjugate        | MV 833 -- Toagosei                         |
| MAB T101-Y-90 conjugate -- Hybritech   | Mycoplasma pulmonis vaccine                |
| MAB T-88 -- Chiron                     | Mycoprex -- XOMA                           |
| MAB TB94 -- Cancer ImmunoBiology       | myeloperoxidase -- Henogen                 |
| MAB TEC 11                             | myostatin -- Genetics Institute            |
| MAB TES-23 -- Chugai                   | Nacolomab tafenatox -- Pharmacia           |
| MAB TM31 -- Avant                      | Nagrecor -- Scios                          |
| MAB TNT-1 -- Cambridge Antibody Tech., | nagrestipen -- British Biotech             |
| Peregrine                              | NAP-5 -- Corvas Intl.                      |
| MAB TNT-3                              | NAPc2 -- Corvas Intl.                      |
| MAB TNT-3 -- IL2 fusion protein --     | nartograstim -- Kyowa                      |
| MAB TP3-At-211                         | Natalizumab -- Protein Design Labs         |
| MAB TP3-PAP conjugate --               | Nateplase -- NIH, Nihon Schering           |
| MAB UJ13A -- ICRT                      | nateplase -- Schering AG                   |
| MAB UN3                                | NBI-3001 -- Neurocrine Biosci.             |
| MAB ZME-018-gelonin conjugate          | NBI-5788 -- Neurocrine Biosci.             |
| MAB-BC2 -- GlaxoSmithKline             | NBI-6024 -- Neurocrine Biosci.             |
| MAB-DM1 conjugate -- ImmunoGen         | Nef inhibitors -- BRI                      |
| MAB-ricin-chain-A conjugate -- XOMA    | Neisseria gonorrhoea vaccine -- Antex      |
| MAB-temoporfin conjugates              | Biologics                                  |
| Monopharm C -- Viventia Biotech        | Neomycin B-arginine conjugate              |
| monteplase -- Eisai                    | Nerelimomab -- Chiron                      |
| montirelin hydrate -- Gruenenthal      | Nerve growth factor -- Amgen -- Chiron,    |
| moroctocog alfa -- Genetics Institute  | Genentech                                  |
| Moroctocog-alfa -- Pharmacia           | Nerve growth factor gene therapy           |
| MP 4                                   | nesiritide citrate -- Scios                |
| MP-121 -- Biopharm                     | neuregulin-2 -- CeNeS                      |
| MP-52 -- Biopharm                      | neurocan -- NYU                            |
| MRA -- Chugai                          | neuronal delivery system -- CAMR           |
| MS 28168 -- Mitsui Chemicals, Nihon    | Neurophil inhibitory Factor -- Corvas      |
| Schering                               | Neuroprotective vaccine -- University of   |
| MSH fusion toxin -- Ligand             | Auckland                                   |
| MSI-99 -- Genaera                      | neurotrophic chimaeras -- Regeneron        |
| MT 201 -- Micromet                     | neurotrophic factor -- NsGene, CereMedix   |

FIG. 28U

52/497

|                                    |                                            |
|------------------------------------|--------------------------------------------|
| NeuroVax -- Immune Response        | Oncophage -- Antigenics                    |
| neurturin -- Genentech             | Oncostatin M -- Bristol-Myers Squibb       |
| neutral endopeptidase -- Genentech | OncoVax-CL -- Jenner Biotherapies          |
| NGF enhancers -- NeuroSearch       | OncoVax-P -- Jenner Biotherapies           |
| NHL vaccine -- Large Scale Biology | oncept -- Yeda                             |
| NIP45 -- Boston Life Sciences      | onychomycosis vaccine -- Boehringer        |
| NKI-B20                            | Ingelheim                                  |
| NM 01 -- Nissin Food               | opebecan -- XOMA                           |
| NMI-139 -- NitroMed                | opioids -- Arizona                         |
| NMMP -- Genetics Institute         | Oprelvekin -- Genetics Institute           |
| NN-2211 -- Novo Nordisk            | Oregovomab -- AltaRex                      |
| Noggin -- Regeneron                | Org-33408 b -- Akzo Nobel                  |
| Nonacog alfa                       | Orolip DP -- EpiCept                       |
| Norelin -- Biostar                 | oryzacystatin                              |
| Norwalk virus vaccine              | OSA peptides -- GenSci Regeneration        |
| NRLU 10 -- NeoRx                   | osteoblast-cadherin GF -- Pharis           |
| NRLU 10 PE -- NeoRx                | Osteocalcin-thymidine kinase gene therapy  |
| NT-3 -- Regeneron                  | osteogenic protein -- Curis                |
| NT-4/5 -- Genentech                | osteopontin -- OraPharma                   |
| NU 3056                            | osteoporosis peptides -- Integra, Telios   |
| NU 3076                            | osteoprotegerin -- Amgen, SnowBrand        |
| NX 1838 -- Gilead Sciences         | otitis media vaccines -- Antex Biologics   |
| NY ESO-1/CAG-3 antigen -- NIH      | ovarian cancer -- University of Alabama    |
| NYVAC-7 -- Aventis Pasteur         | OX40-IgG fusion protein -- Cantab, Xenova  |
| NZ-1002 -- Novazyme                | P 246 -- Diatide                           |
| obesity therapy -- Nobex           | P 30 -- Alfacell                           |
| OC 10426 -- Ontogen                | p1025 -- Active Biotech                    |
| OC 144093 -- Ontogen               | P-113 <sup>A</sup> -- Demegen              |
| OCIF -- Sankyo                     | P-16 peptide -- Transition Therapeutics    |
| Oct-43 -- Otsuka                   | p43 -- Ramot                               |
| Odulimomab -- Immunotech           | P-50 peptide -- Transition Therapeutics    |
| OK PSA - liposomal                 | p53 + RAS vaccine -- NIH, NCI              |
| OKT3-gamma-1-ala-ala               | PACAP(1-27) analogue                       |
| OM 991                             | paediatric vaccines -- Chiron              |
| OM 992                             | Pafase -- ICOS                             |
| Omalizumab -- Genentech            | PAGE-4 plasmid DNA -- IDEC                 |
| oncoimmunin-L -- NIH               | PAI-2 -- Biotech Australia, Human          |
| Oncolysin B -- ImmunoGen           | Therapeutics                               |
| Oncolysin CD6 -- ImmunoGen         | Palifermin (keratinocyte growth factor) -- |
| Oncolysin M -- ImmunoGen           | Amgen                                      |
| Oncolysin S -- ImmunoGen           | Palivizumab -- MedImmune                   |

**FIG. 28V**

53/497

|                                           |                                           |
|-------------------------------------------|-------------------------------------------|
| PAM 4 -- Merck                            | PEG-uricase -- Mountain View              |
| pamiteplase -- Yamanouchi                 | Pegvisomant -- Genentech                  |
| pancreatin, Minitabs -- Eurand            | PEGylated proteins, PolyMASC -- Valentis  |
| Pangen -- Fournier                        | PEGylated recombinant native human leptin |
| Pantarin -- Selective Genetics            | -- Roche                                  |
| Parainfluenza virus vaccine -- Pharmacia, | Pentumomab                                |
| Pierre Fabre                              | Penetratin -- Cyclacel                    |
| paraoxanase -- Esperion                   | Pepscan -- Antisoma                       |
| parathyroid hormone -- Abiogen, Korea     | peptide G -- Peptech, ICRT                |
| Green Cross                               | peptide vaccine -- NIH, NCI               |
| Parathyroid hormone (1-34) --             | Pexelizumab                               |
| Chugai/Suntory                            | pexiganan acetate -- Genaera              |
| Parkinson's disease gene therapy -- Cell  | Pharmaprojects No. 3179 -- NYU            |
| Genesys/ Ceregene                         | Pharmaprojects No. 3390 -- Ernest Orlando |
| Parvovirus vaccine -- MedImmune           | Pharmaprojects No. 3417 -- Sumitomo       |
| PCP-Scan -- Immunomedics                  | Pharmaprojects No. 3777 -- Acambis        |
| PDGF -- Chiron                            | Pharmaprojects No. 4209 -- XOMA           |
| PDGF cocktail -- Theratechnologies        | Pharmaprojects No. 4349 -- Baxter Intl.   |
| peanut allergy therapy -- Dynavax         | Pharmaprojects No. 4651                   |
| PEG anti-ICAM MAb -- Boehringer           | Pharmaprojects No. 4915 -- Avanir         |
| Ingelheim                                 | Pharmaprojects No. 5156 -- Rhizogenics    |
| PEG asparaginase -- Enzon                 | Pharmaprojects No. 5200 -- Pfizer         |
| PEG glucocerebrosidase                    | Pharmaprojects No. 5215 -- Origene        |
| PEG hirudin -- Knoll                      | Pharmaprojects No. 5216 -- Origene        |
| PEG interferon-alpha-2a -- Roche          | Pharmaprojects No. 5218 -- Origene        |
| PEG interferon-alpha-2b + ribavirin --    | Pharmaprojects No. 5267 -- ML             |
| Biogen, Enzon, ICN Pharmaceuticals,       | Laboratories                              |
| Schering-Plough                           | Pharmaprojects No. 5373 -- MorphoSys      |
| PEG MAb A5B7 --                           | Pharmaprojects No. 5493 -- Metabolex      |
| Pegacaristim -- Amgen -- Kirin Brewery -- | Pharmaprojects No. 5707 -- Genentech      |
| ZymoGenetics                              | Pharmaprojects No. 5728 -- Autogen        |
| Pegaldesleukin -- Research Corp           | Pharmaprojects No. 5733 -- BioMarin       |
| pegaspargase -- Enzon                     | Pharmaprojects No. 5757 -- NIH            |
| pegfilgrastim -- Amgen                    | Pharmaprojects No. 5765 -- Gryphon        |
| PEG-interferon Alpha -- Viragen           | Pharmaprojects No. 5830 -- AntiCancer     |
| PEG-interferon Alpha 2A -- Hoffman La-    | Pharmaprojects No. 5839 -- Dyax           |
| Roche                                     | Pharmaprojects No. 5849 -- Johnson &      |
| PEG-interferon Alpha 2B -- Schering-      | Johnson                                   |
| Plough                                    | Pharmaprojects No. 5860 -- Mitsubishi-    |
| PEG-r-hirudin -- Abbott                   | Tokyo                                     |
| PEG-rHuMGDF -- Amgen                      |                                           |

FIG. 28W

54/497

|                                                                                                               |                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharmaprojects No. 5869 -- Oxford GlycoSciences                                                               | Plasminogen activators -- Abbott Laboratories, American Home Products, Boehringer Mannheim, Chiron                                                                                          |
| Pharmaprojects No. 5883 -- Asahi Brewery                                                                      | Corporation, DuPont Pharmaceuticals, Eli Lilly, Shionogi, Genentech, Genetics Institute, GlaxoSmithKline, Hemispherx Biopharma, Merck & Co, Novartis, Pharmacia Corporation, Wakamoto, Yeda |
| Pharmaprojects No. 5947 -- StressGen                                                                          | plasminogen-related peptides -- Bio-Tech. General/MGH                                                                                                                                       |
| Pharmaprojects No. 5961 -- Theratechnologies                                                                  | platelet factor 4 -- RepliGen                                                                                                                                                               |
| Pharmaprojects No. 5962 -- NIH                                                                                | Platelet-derived growth factor -- Amgen -- ZymoGenetics                                                                                                                                     |
| Pharmaprojects No. 5966 -- NIH                                                                                | plusonemin-- Hayashibara                                                                                                                                                                    |
| Pharmaprojects No. 5994 -- Pharming                                                                           | PMD-2850 -- Protherics                                                                                                                                                                      |
| Pharmaprojects No. 5995 -- Pharming                                                                           | Pneumococcal vaccine -- Antex Biologics, Aventis Pasteur                                                                                                                                    |
| Pharmaprojects No. 6023 -- IMMUCON                                                                            | Pneumococcal vaccine intranasal -- BioChem Vaccines/Biovector                                                                                                                               |
| Pharmaprojects No. 6063 -- Cytoclonal                                                                         | PR1A3                                                                                                                                                                                       |
| Pharmaprojects No. 6073 -- SIDDCO                                                                             | PR-39                                                                                                                                                                                       |
| Pharmaprojects No. 6115 -- Genzyme                                                                            | pralmorelin -- Kaken                                                                                                                                                                        |
| Pharmaprojects No. 6227 -- NIH                                                                                | Pretarget-Lymphoma -- NeoRx                                                                                                                                                                 |
| Pharmaprojects No. 6230 -- NIH                                                                                | Priliximab -- Centocor                                                                                                                                                                      |
| Pharmaprojects No. 6236 -- NIH                                                                                | PRO 140 -- Progenics                                                                                                                                                                        |
| Pharmaprojects No. 6243 -- NIH                                                                                | PRO 2000 -- Procept                                                                                                                                                                         |
| Pharmaprojects No. 6244 -- NIH                                                                                | PRO 367 -- Progenics                                                                                                                                                                        |
| Pharmaprojects No. 6281 -- Senetek                                                                            | PRO 542 -- Progenics                                                                                                                                                                        |
| Pharmaprojects No. 6365 -- NIH                                                                                | pro-Apo A-I -- Esperion                                                                                                                                                                     |
| Pharmaprojects No. 6368 -- NIH                                                                                | prolactin -- Genzyme                                                                                                                                                                        |
| Pharmaprojects No. 6373 -- NIH                                                                                | Prosaptide TX14(A) -- Bio-Tech. General                                                                                                                                                     |
| Pharmaprojects No. 6408 -- Pan Pacific                                                                        | prostate cancer antibodies -- Immunex, UroCor                                                                                                                                               |
| Pharmaprojects No. 6410 -- Athersys                                                                           | prostate cancer antibody therapy -- Genentech/UroGenesys, Genotherapeutics                                                                                                                  |
| Pharmaprojects No. 6421 -- Oxford GlycoSciences                                                               | prostate cancer immunotherapeutics -- The PSMA Development Company                                                                                                                          |
| Pharmaprojects No. 6522 -- Maxygen                                                                            | prostate cancer vaccine -- Aventis Pasteur, Zonagen, Corixa, Dendreon, Jenner                                                                                                               |
| Pharmaprojects No. 6523 -- Pharis                                                                             | Biotherapies, Therion Biologics                                                                                                                                                             |
| Pharmaprojects No. 6538 -- Maxygen                                                                            |                                                                                                                                                                                             |
| Pharmaprojects No. 6554 -- APALEXO                                                                            |                                                                                                                                                                                             |
| Pharmaprojects No. 6560 -- Ardana                                                                             |                                                                                                                                                                                             |
| Pharmaprojects No. 6562 -- Bayer                                                                              |                                                                                                                                                                                             |
| Pharmaprojects No. 6569 -- Eos                                                                                |                                                                                                                                                                                             |
| Phenoxazine                                                                                                   |                                                                                                                                                                                             |
| Phenylase -- Ibex                                                                                             |                                                                                                                                                                                             |
| Pigment epithelium derived factor -- plasminogen activator inhibitor-1, recombinant -- DuPont Pharmaceuticals |                                                                                                                                                                                             |

FIG. 28X

55/497

|                                              |                                              |
|----------------------------------------------|----------------------------------------------|
| prostate-specific antigen -- EntreMed        | RD 62198                                     |
| protein A -- RepliGen                        | rDnase -- Genentech                          |
| protein adhesives -- Enzon                   | RDP-58 -- SangStat                           |
| protein C -- Baxter Intl., PPL Therapeutics, | RecepTox-Fce -- Keryx                        |
| ZymoGenetics                                 | RecepTox-GnRH -- Keryx, MTR                  |
| protein C activator -- Gilead Sciences       | Technologies                                 |
| protein kinase R antags -- NIH               | RecepTox-MBP -- Keryx, MTR                   |
| protirelin -- Takeda                         | Technologies                                 |
| protocadherin 2 -- Caprion                   | recFSH -- Akzo Nobel, Organon                |
| Pro-urokinase -- Abbott, Bristol-Myers       | REGA 3G12                                    |
| Squibb, Dainippon, Tosoh -- Welfide          | Regavirumab -- Teijin                        |
| P-selectin glycoprotein ligand-1 -- Genetics | relaxin -- Connetics Corp                    |
| Institute                                    | Renal cancer vaccine -- Macropharm           |
| pseudomonal infections -- InterMune          | repifermin -- Human Genome Sciences          |
| Pseudomonas vaccine -- Cytovax               | Respiratory syncytial virus PFP-2 vaccine -- |
| PSGL-Ig -- American Home Products            | Wyeth-Lederle                                |
| PSP-94 -- Procyon                            | Respiratory syncytial virus vaccine --       |
| PTH 1-34 -- Nobex                            | GlaxoSmithKline, Pharmacia, Pierre Fabre     |
| Quilimmune-M -- Antigenics                   | Respiratory syncytial virus vaccine          |
| R 744 -- Roche                               | inactivated                                  |
| R 101933                                     | Respiratory syncytial virus-parainfluenza    |
| R 125224 -- Sankyo                           | virus vaccine -- Aventis Pasteur,            |
| RA therapy -- Cardion                        | Pharmacia                                    |
| Rabies vaccine recombinant -- Aventis        | Reteplase -- Boehringer Mannheim,            |
| Pasteur, BioChem Vaccines, Kaketsuken        | Hoffman La-Roche                             |
| Pharmaceuticals                              | Retropep -- Retroscreen                      |
| RadioTheraCIM -- YM BioSciences              | RFB4 (dsFv) PE38                             |
| Ramot project No. 1315 -- Ramot              | RFI 641 -- American Home Products            |
| Ramot project No. K-734A -- Ramot            | RFTS -- UAB Research Foundation              |
| Ramot project No. K-734B -- Ramot            | RG 12986 -- Aventis Pasteur                  |
| Ranibizumab (Anti-VEGF fragment) --          | RG 83852 -- Aventis Pasteur                  |
| Genentech                                    | RG-1059 -- RepliGen                          |
| RANK -- Immunex                              | rGCR -- NIH                                  |
| ranpirnase -- Alfacell                       | rGLP-1 -- Restoragen                         |
| ranpirnase-anti-CD22 MAb -- Alfacell         | rGRF -- Restoragen                           |
| RANTES inhibitor -- Milan                    | rh Insulin -- Eli Lilly                      |
| RAPID drug delivery systems -- ARIAD         | RHAMM targeting peptides -- Cangene          |
| rasburicase -- Sanofi                        | rHb1.1 -- Baxter Intl.                       |
| rBPI-21, topical -- XOMA                     | rhCC10 -- Claragen                           |
| RC 529 -- Corixa                             | rhCG -- Serono                               |
| rCFTR -- Genzyme Transgenics                 | Rheumatoid arthritis gene therapy            |

FIG. 28Y

56/497

|                                                                 |                                                          |
|-----------------------------------------------------------------|----------------------------------------------------------|
| Rheumatoid arthritis vaccine -- Veterans Affairs Medical Center | SB RA 31012 --                                           |
| rhLH -- Serono                                                  | SC 56929 -- Pharmacia                                    |
| Ribozyme gene therapy -- Genset                                 | SCA binding proteins -- Curis, Enzon                     |
| Rickettsial vaccine recombinant                                 | scFv(14E1)-ETA Berlex Laboratories, Schering AG          |
| RIGScan CR -- Neoprobe                                          | ScFv(FRP5)-ETA --                                        |
| RIP-3 -- Rigel                                                  | ScFv6C6-PE40 --                                          |
| Rituximab -- Genentech                                          | SCH 55700 -- Celltech                                    |
| RK-0202 -- RxKinetix                                            | Schistosomiasis vaccine -- Glaxo Wellcome/Medeva, Brazil |
| RLT peptide -- Esperion                                         | SCPF -- Advanced Tissue Sciences                         |
| rM/NEI -- IVAX                                                  | scuPA-suPAR complex -- Hadasit                           |
| rmCRP -- Immtech                                                | SD-9427 -- Pharmacia                                     |
| RN-1001 -- Renovo                                               | SDF-1 -- Ono                                             |
| RN-3 -- Renovo                                                  | SDZ 215918 -- Novartis                                   |
| RNase conjugate -- Immunomedics                                 | SDZ 280125 -- Novartis                                   |
| RO 631908 -- Roche                                              | SDZ 89104 -- Novartis                                    |
| Rotavirus vaccine -- Merck                                      | SDZ ABL 364 -- Novartis                                  |
| RP 431 -- DuPont Pharmaceuticals                                | SDZ MMA 383 -- Novartis                                  |
| RP-128 -- Resolution                                            | Secretin -- Ferring, Repligen                            |
| RPE65 gene therapy --                                           | serine protease inhbs -- Pharls                          |
| RPR 110173 -- Aventis Pasteur                                   | sermorelin acetate -- Serono                             |
| RPR 115135 -- Aventis Pasteur                                   | SERP-1 -- Viron                                          |
| RPR 116258A -- Aventis Pasteur                                  | sertenef -- Daiinippon                                   |
| rPSGL-Ig -- American Home Products                              | serum albumin, Recombinant human -- Aventis Behring      |
| r-SPC surfactant -- Byk Gulden                                  | serum-derived factor -- Hadasit                          |
| RSV antibody -- Medimmune                                       | Sevirumab -- Novartis                                    |
| Ruplizumab -- Biogen                                            | SGN 14 -- Seattle Genetics                               |
| rV-HER-2/neu -- Therion Biologics                               | SGN 15 -- Seattle Genetics                               |
| SA 1042 -- Sankyo                                               | SGN 17/19 -- Seattle Genetics                            |
| sacrosidase -- Orphan Medical                                   | SGN 30 -- Seattle Genetics                               |
| Sant 7                                                          | SGN-10 -- Seattle Genetics                               |
| Sargramostim -- Immunex                                         | SGN-11 -- Seattle Genetics                               |
| saruplase -- Gruenenthal                                        | SH 306 -- DuPont Pharmaceuticals                         |
| Satumomab -- Cytogen                                            | Shanvac-B -- Shantha                                     |
| SB 1 -- COR Therapeutics                                        | Shigella flexneri vaccine -- Avant, Acambis, Novavax     |
| SB 207448 -- GlaxoSmithKline                                    | Shigella sonnei vaccine --                               |
| SB 208651 -- GlaxoSmithKline                                    | slCAM-1 -- Boehringer Ingelheim                          |
| SB 240683 -- GlaxoSmithKline                                    | Silteplase -- Genzyme                                    |
| SB 249415 -- GlaxoSmithKline                                    |                                                          |
| SB 249417 -- GlaxoSmithKline                                    |                                                          |
| SB 6 -- COR Therapeutics                                        |                                                          |

FIG. 28Z

57/497

|                                                |                                              |
|------------------------------------------------|----------------------------------------------|
| SIV vaccine -- Endocon, Institut Pasteur       | Staphylococcus aureus vaccine conjugate --   |
| SK 896 -- Sanwa Kagaku Kenkyusho               | Nabi                                         |
| SK-827 -- Sanwa Kagaku Kenkyusho               | Staphylococcus therapy -- Tripep             |
| Skeletex -- CellFactors                        | Staphylokinase -- Biovation, Prothera,       |
| SKF 106160 -- GlaxoSmithKline                  | Thrombogenetics                              |
| S-nitroso-AR545C --                            | Streptococcal A vaccine -- M6                |
| SNTP -- Active Biotech                         | Pharmaceuticals, North American Vaccine      |
| somatomedin-1 -- GroPep, Mitsubishi-           | Streptococcal B vaccine -- Microscience      |
| Tokyo, NIH                                     | Streptococcal B vaccine recombinant --       |
| somatomedin-1 carrier protein -- Insmmed       | Biochem Vaccines                             |
| somatostatin -- Ferring                        | Streptococcus pyogenes vaccine               |
| Somatotropin/                                  | STRL-33 -- NIH                               |
| Human Growth Hormone -- Bio-Tech.              | Subalin -- SRC VB VECTOR                     |
| General, Eli Lilly                             | SUIS -- United Biomedical                    |
| somatropin -- Bio-Tech. General, Alkermes,     | SUIS-LHRH -- United Biomedical               |
| ProLease, Aventis Behring, Biovector,          | SUN-E3001 -- Suntory                         |
| Cangene, Dong-A, Eli Lilly, Emisphere,         | super high affinity monoclonal antibodies -- |
| Enact, Genentech, Genzyme Transgenics,         | YM BioSciences                               |
| Grandis/InfiMed, CSL, InfiMed, MacroMed,       | Superoxide dismutase -- Chiron, Enzon,       |
| Novartis, Novo Nordisk, Pharmacia              | Ube Industries, Bio-Tech, Yeda               |
| Serono, TranXenoGen                            | superoxide dismutase-2 -- OXIS               |
| somatropin derivative -- Schering AG           | suppressin -- UAB Research Foundation        |
| somatropin, AIR -- Eli Lilly                   | SY-161-P5 -- ThromboGenics                   |
| Somatropin, inhaled -- Eli Lilly/Alkermes      | SY-162 -- ThromboGenics                      |
| somatropin, Kabi -- Pharmacia                  | Systemic lupus erythematosus vaccine --      |
| somatropin, Orasome -- Novo Nordisk            | MedClone/VivoRx                              |
| Sonermin -- Dainippon Pharmaceutical           | T cell receptor peptides -- Xoma             |
| SP(V5.2)C -- Supertek                          | T cell receptor peptide vaccine              |
| SPf66                                          | T4N5 liposomes -- AGI Dermatics              |
| sphingomyelinase -- Genzyme                    | TAC1, soluble -- ZymoGenetics                |
| SR 29001 -- Sanofi                             | targeted apoptosis -- Antisoma               |
| SR 41476 -- Sanofi                             | tasonermin -- Boehringer Ingelheim           |
| SR-29001 -- Sanofi                             | TASP                                         |
| SS1(dsFV)-PE38 -- NeoPharm                     | TASP-V                                       |
| $\beta$ 2 microglobulin -- Avidex              | Tat peptide analogues -- NIH                 |
| $\beta$ 2-microglobulin fusion proteins -- NIH | TBP I -- Yeda                                |
| $\beta$ -amyloid peptides -- CeNeS             | TBP II                                       |
| $\beta$ -defensin -- Pharis                    | TBV25H -- NIH                                |
| Staphylococcus aureus infections --            | Tc 99m for cea1 -- Center of Molecular       |
| Inhibitex/ZLB                                  | Immunology                                   |
|                                                | Tc 99m P 748 -- Diatide                      |

FIG. 28AA

58/497

|                                           |                                           |
|-------------------------------------------|-------------------------------------------|
| Tc 99m votumumab -- Intracell             | Tissue factor -- Genentech                |
| Tc-99m rh-Annexin V -- Theseus Imaging    | Tissue factor pathway inhibitor           |
| teceleukin -- Biogen                      | TJN-135 -- Tsumura                        |
| tenecteplase -- Genentech                 | TM 27 -- Avant                            |
| Teriparatide -- Armour Pharmaceuticals,   | TM 29 -- Avant                            |
| Asahi Kasei, Eli Lilly                    | TMC-151 -- Tanabe Seiyaku                 |
| terlipressin -- Ferring                   | TNF tumour necrosis factor -- Asahi Kasei |
| testisin -- AMRAD                         | TNF Alpha -- CytImmune                    |
| Tetra fibrin -- Roche                     | TNF antibody -- Johnson & Johnson         |
| TFPI -- EntreMed                          | TNF binding protein -- Amgen              |
| tgD-IL-2 -- Takeda                        | TNF degradation product -- Oncotech       |
| TGF-Alpha -- ZymoGenetics                 | TNF receptor -- Immunex                   |
| TGF- $\beta$ -- Kolon                     | TNF receptor 1; soluble -- Amgen          |
| TGF- $\beta$ 2 -- Insmed                  | TNF Tumour necrosis factor-alpha -- Asahi |
| TGF- $\beta$ 3 -- OSI                     | Kasei, Genentech, Mochida                 |
| Thalassaemia gene therapy -- Crucell      | TNF-Alpha inhibitor -- Tripep             |
| TheraCIM-h-R3 -- Center of Molecular      | TNFR:Fc gene therapy -- Targeted Genetics |
| Immunology, YM BioSciences                | TNF-SAM2                                  |
| Theradigm-HBV -- Epimmune                 | Tolerimab -- Innogenetics                 |
| Theradigm-HPV -- Epimmune                 | Toxoplasma gondii vaccine --              |
| Theradigm-malaria -- Epimmune             | GlaxoSmithKline                           |
| Theradigm-melanoma -- Epimmune            | TP 9201 -- Telios                         |
| TheraFab -- Antisoma                      | TP10 -- Avant                             |
| ThGRF 1-29 -- Theratechnologies           | TP20 -- Avant                             |
| ThGRF 1-44 -- Theratechnologies           | tPA -- Centocor                           |
| Thrombin receptor activating peptide --   | trafermin -- Scios                        |
| Abbott                                    | TRAIL/Apo2L -- Immunex                    |
| thrombomodulin -- Iowa, Novocastra        | TRAIL-R1 MAb -- Cambridge Antibody        |
| Thrombopoietin -- Dragon Pharmaceuticals, | Technologies                              |
| Genentech                                 | transferrin-binding proteins -- CAMR      |
| thrombopoietin, Pliva -- Recepton         | Transforming growth factor-beta-1 --      |
| Thrombospondin 2 --                       | Genentech                                 |
| thrombostatin -- Thromgen                 | transport protein -- Genesis              |
| thymalfasin -- SciClone                   | Trastuzumab -- Genentech                  |
| thymocartin -- Gedeon Richter             | TRH -- Ferring                            |
| thymosin Alpha1 -- NIH                    | Triabin -- Schering AG                    |
| thyroid stimulating hormone -- Genzyme    | Triconal                                  |
| tICAM-1 -- Bayer                          | Triflavin                                 |
| Tick anticoagulant peptide -- Merck       | troponin I -- Boston Life Sciences        |
| TIF -- Xoma                               | TRP-2 <sup>A</sup> -- NIH                 |
| Tifacogin -- Chiron, NIS, Pharmacia       | trypsin inhibitor -- Mochida              |

FIG. 28BB

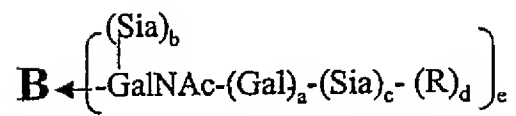
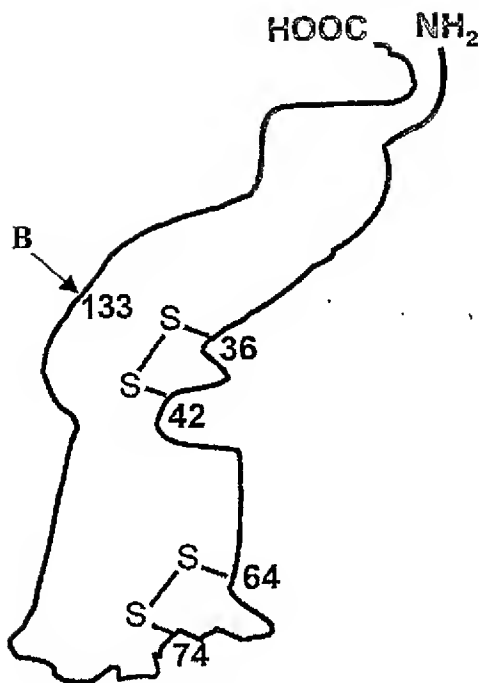


59/497

|                                              |                                            |
|----------------------------------------------|--------------------------------------------|
| TSP-1 gene therapy –                         | Vascular endothelial growth factors – R&D  |
| TT-232                                       | Systems                                    |
| TTS-CD2 – Active Biotech                     | vascular targeting agents – Peregrine      |
| Tuberculosis vaccine – Aventis Pasteur,      | vasopermeation enhancement agents --       |
| Genesis                                      | Peregrine                                  |
| Tumor Targeted Superantigens – Active        | vasostatin – NIH                           |
| Biotech – Pharmacia                          | VCL – Bio-Tech. General                    |
| tumour vaccines – PhotoCure                  | VEGF – Genentech, Scios                    |
| tumour-activated prodrug antibody            | VEGF inhibitor – Chugai                    |
| conjugates – Millennium/ImmunoGen            | VEGF-2 – Human Genome Sciences             |
| tumstatin – ILEX                             | VEGF-Trap – Regeneron                      |
| Tuvirumab – Novartis                         | viscumin, recombinant – Madaus             |
| TV-4710 – Teva                               | Vitaxin                                    |
| TWEAK receptor -- Immunex                    | Vitrax -- ISTA Pharmaceuticals             |
| TXU-PAP                                      | West Nile virus vaccine -- Bavarian Nordic |
| TY-10721 – TOA Eiyo                          | WP 652                                     |
| Type I diabetes vaccine -- Research Corp     | WT1 vaccine -- Corixa                      |
| Typhoid vaccine CVD 908                      | WX-293 – Willex BioTech.                   |
| U 143677 -- Pharmacia                        | WX-360 -- Willex BioTech.                  |
| U 81749 -- Pharmacia                         | WX-UK1 – Willex BioTech.                   |
| UA 1248 – Arizona                            | XMP-500 – XOMA                             |
| UGIF – Sheffield                             | XomaZyme-791 – XOMA                        |
| UIC 2                                        | XTL 001 – XTL Biopharmaceuticals           |
| UK 101                                       | XTL 002 – XTL Biopharmaceuticals           |
| UK-279276 – Corvas Intl.                     | yeast delivery system -- GlobelImmune      |
| urodilatin – Pharis                          | Yersinia pestis vaccine                    |
| urofollitrophin – Serono                     | YIGSR-Stealth – Johnson & Johnson          |
| Urokinase – Abbott                           | Yisum Project No. D-0460 -- Yisum          |
| uteroferrin-- Pepgen                         | YM 207 – Yamanouchi                        |
| V 20 – GLYCODesign                           | YM 337 -- Protein Design Labs              |
| V2 vasopressin receptor gene therapy         | Yttrium-90 labelled biotin                 |
| vaccines -- Active Biotech                   | Yttrium-90-labeled anti-CEA MAb T84.66 –   |
| Varicella zoster glycoprotein vaccine --     | ZD 0490 – AstraZeneca                      |
| Research Corporation Technologies            | ziconotide – Elan                          |
| Varicella zoster virus vaccine live – Cantab | ZK 157138 -- Berlex Laboratories           |
| Pharmaceuticals                              | Zolimomab aritox                           |
| Vascular endothelial growth factor –         | Zorcell – Immune Response                  |
| Genentech, University of California          | ZRXL peptides – Novartis                   |

FIG. 28CC

60/497



a-c, e (independently selected) = 0 or 1;  
 d = 0;  
 R = modifying group, sialyl or  
 oligosialyl

FIG. 29A

61/497

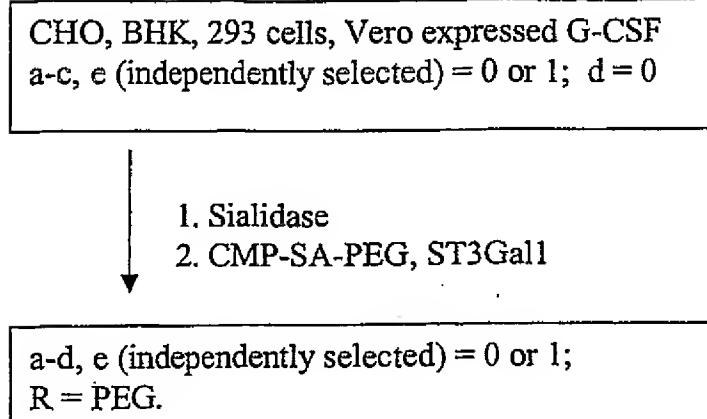


FIG. 29B

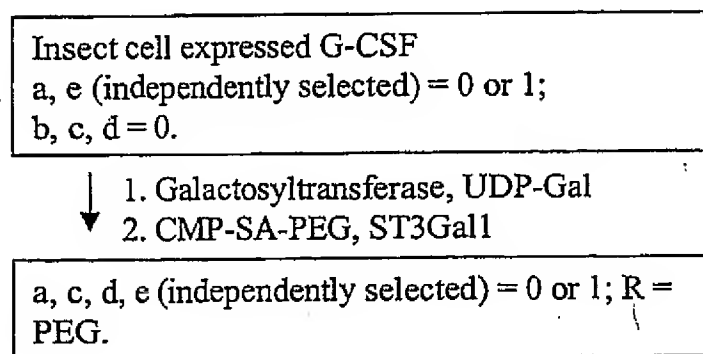


FIG. 29C

62/497

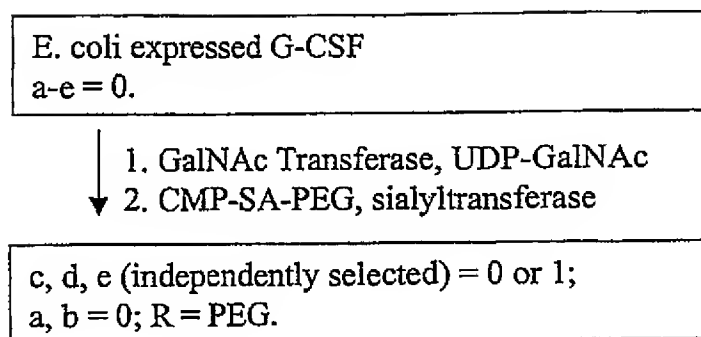


FIG. 29D

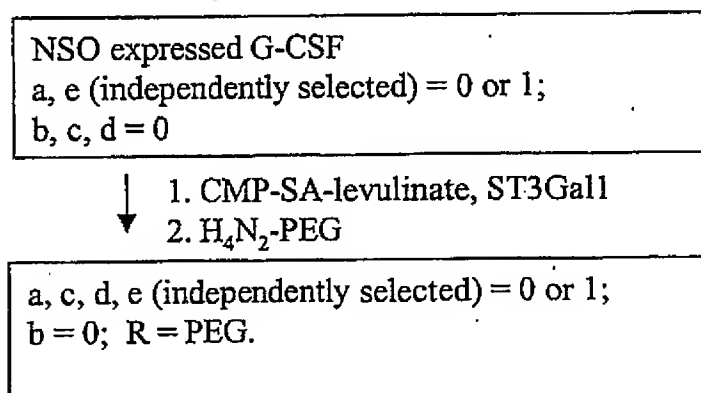


FIG. 29E

63/497

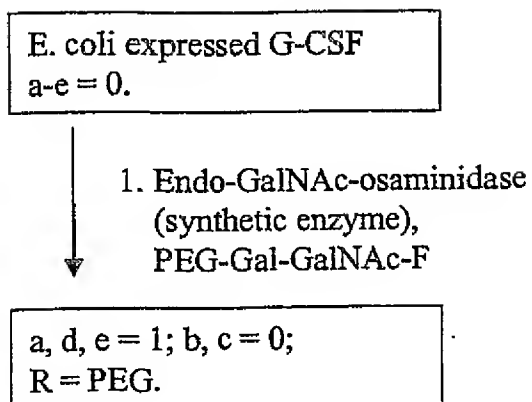


FIG. 29F

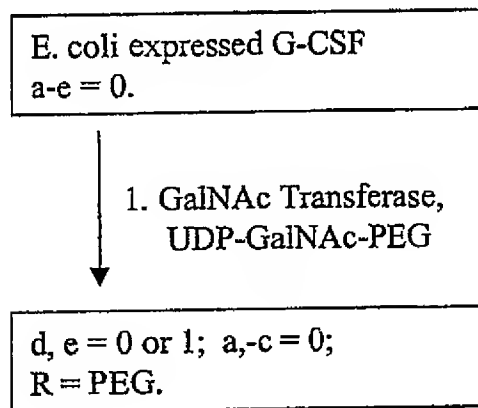
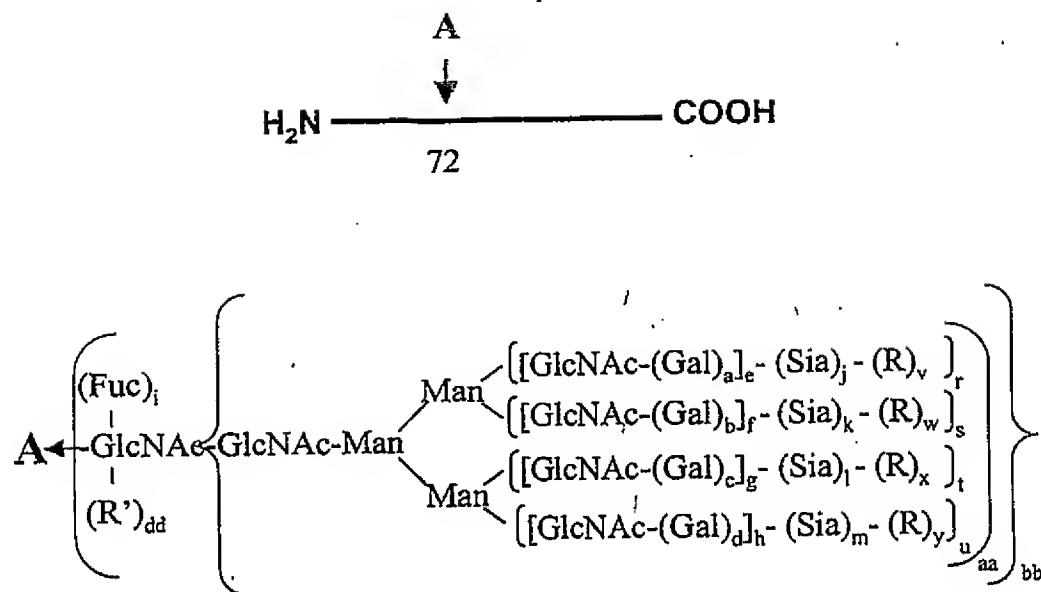


FIG. 29G

64/497



a-d, i, n-u (independently selected) = 0 or 1.

aa, bb, cc, dd, ee (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 6.

j-m (independently selected) = 0 to 20.

v-z = 0; R = modifying group, mannose, oligo-mannose.

R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 30A

65/497

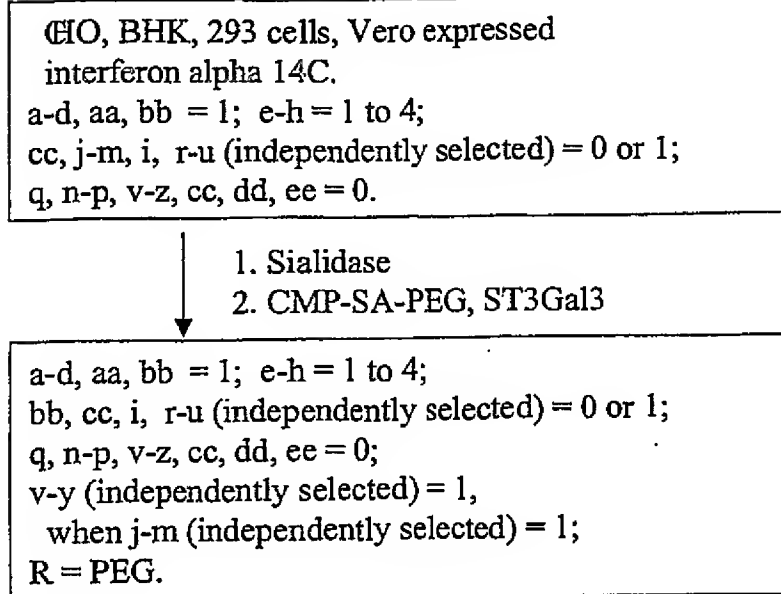


FIG. 30B

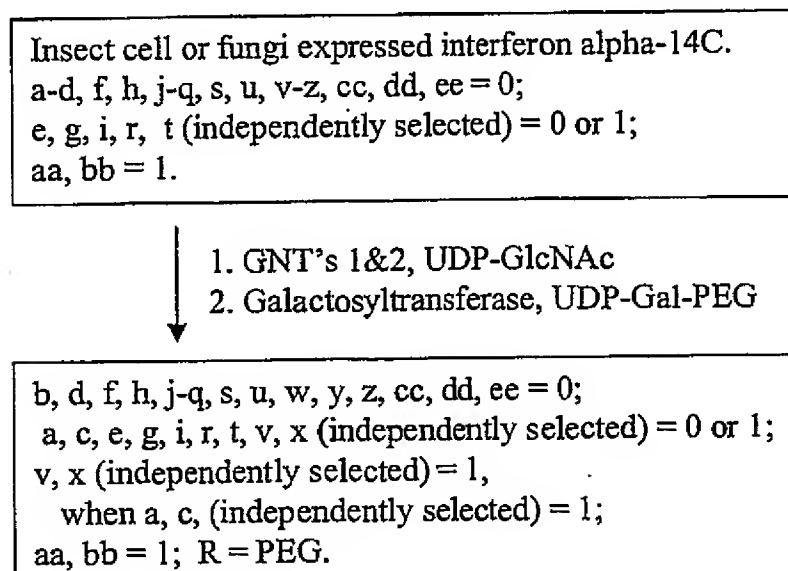


FIG. 30C

66/497

Yeast expressed interferon alpha-14C.  
a-q, cc, dd, ee, v-z = 0;  
r-y (independently selected) = 0 to 1;  
aa, bb = 1;  
R (branched or linear) = Man, oligomannose or  
polysaccharide.

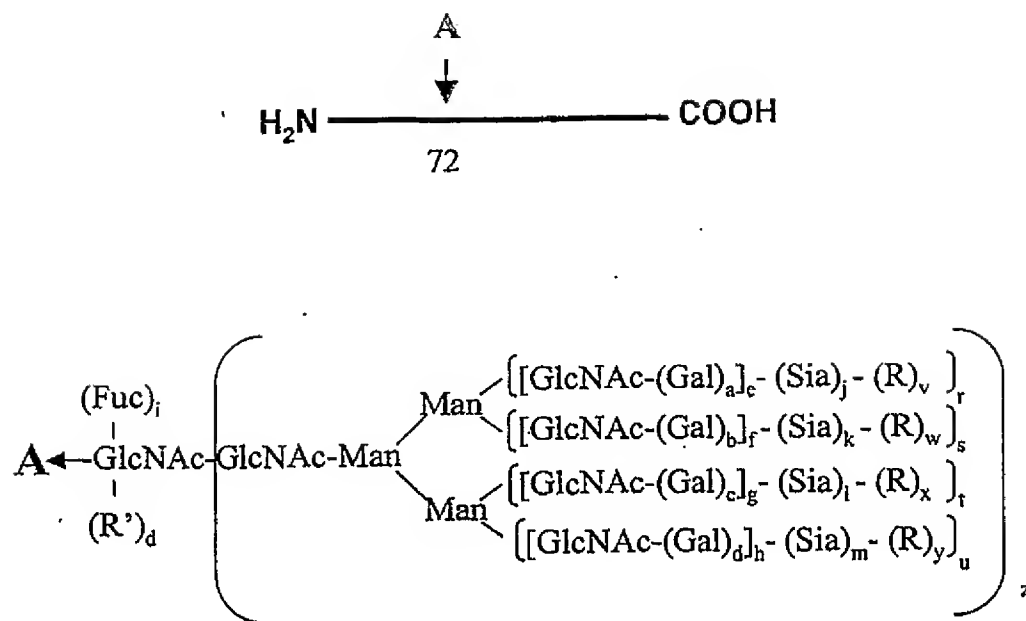
- ↓  
1. Endo-H  
2. Galactosyltransferase, UDP-Gal  
3.. CMP-SA-PEG, ST3Gal3

a-z, bb = 0; aa = 1; R' = -Gal-Sia-PEG.

FIG. 30D



67/497



a-d, i, r-u (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 4.

j-m (independently selected) = 0 or 1.

n, v-y = 0; z = 0 or 1.

R = polymer; R' = sugar, glycoconjugate.

FIG. 30E

68/497

CHO, BHK, 293 cells, Vero expressed  
interferon alpha-14C.  
h = 1 to 3;  
a-g, j-m, i (independently selected) = 0 or 1;  
r-u (independently selected) = 0 or 1;  
n, v-y = 0; z = 1.



1. CMP-SA-PEG, ST3Gal3

h = 1 to 3;  
a-g, i (independently selected) = 0 or 1;  
r-u (independently selected) = 0 or 1;  
j-m, v-y (independently selected) = 0 or 1;  
z = 1; n = 0; R = PEG.

FIG. 30F

Insect cell or fungi expressed  
interferon alpha-14C.  
a-d, f, h, j-n, s, u, v-y = 0;  
e, g, i, r, t (independently selected) = 0 or 1;  
z = 1.



1. GNT's 1,2,4,5, UDP-GlcNAc  
2. Galactosyltransferase, UDP-Gal  
3. CMP-SA-PEG, ST3Gal3

a-m, r-y (independently selected) = 0 or 1;  
z = 1; n = 0; R = PEG.

FIG. 30G

69/497

Yeast expressed interferon alpha-14C.

a-n = 0; r-y (independently selected) = 0 to 1;  
z = 1; R (branched or linear) = Man,  
oligomannose.

1. mannosidases
2. GNT's 1,2,4,5, UDP-GlcNAc
3. Galactosyltransferase, UDP-Gal
4. CMP-SA-PEG, ST3Gal3

a-m, r-y (independently selected) = 0 or 1;  
z = 1; n = 0; R = PEG.

FIG. 30H

NSO expressed interferon alpha 14C.

a-i, r-u (independently selected) = 0 or 1;  
j-m, n, v-y = 0; z = 1.

1. CMP-SA-levulinate, ST3Gal3,  
buffer, salt
2. H<sub>4</sub>N<sub>2</sub>-PEG

a-i, j-m, r-y (independently selected) = 0 or 1;  
n = 0; z = 1; R = PEG.

FIG. 30I